The Journal of Pediatrics

VOL. 33 SEPTEMBER, 1948 NO. 3

Original Communications

HYALURONIDASE IN FLUID ADMINISTRATION

A PRELIMINARY REPORT

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THE administration of fluids to infants and young children has always been a problem. To give them intravenously frequently meant a cutdown which involved further trauma to a usually very sick infant, and even that was at times difficult in cases of circulatory collapse and shock.

Subcutaneously, fluids could be given easily enough but not in great enough quantities nor repeatedly in the same area, due to the great distention and trauma to the tissues.

Certainly a method or drug to facilitate clysis would be helpful to the pediatrician treating dehydrated babies. Recently several hopeful reports[1-3] have appeared on the use of hyaluronidase, a drug which may be the answer to this problem.

In their papers Sannella[1] and Hechter[2] showed that this enzyme increased the rate of fluid absorption twelve times. This action was explained by the fact that hyaluronidase, a mucolytic enzyme,[4] acts on and depolymerizes the mucopolysaccharide, hyaluronic acid. This is the gel present in the ground substance of connective tissue, which acts as a tissue barrier to fluid diffusion.

In Sannella and Hechter's work on rabbits,[1, 2] guinea pigs,[3] and twelve human volunteers,[2] the only untoward effect noted was a slight transient erythema at the site of injection, occurring a few hours after use and associated with a dull, aching pain. However, in these reports only the effect on the blood count, blood pressure, and pulse was studied.

Since this drug* has tremendous potentialities in fluid administration, it was decided that further and more detailed studies should be undertaken to determine the full safety of the drug and to determine whether it would make clysis potent enough to decrease the number of intravenous injections necessary.

First, six individuals (four children and two adults) were studied from the standpoint of the effect of hyaluronidase administration on the urine, blood

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*The hyaluronidase was supplied through the courtesy of Dr. J. C. Winter, Director of Clinical Research of G. D. Searle Co., Chicago, Ill.

count, sedimentation rate, cholesterol, phosphorous, proteins, urea nitrogen, creatinin, sugar, icteric index, van den Bergh, and cephalin flocculation tests.

These tests were done before and twenty-four hours after the administration of 0.02 mg. (0.2 c.c. of 100 μg per cubic centimeter) of hyaluronidase to each individual, and the results are summarized in Table I.

TABLE I. EFFECT OF HYALURONIDASE INJECTIONS

	BEFORE	AFTER
Number of subjects	6	6
Sugar	94-111 mg. %	83-119 mg. %
Urea	12.4-19.5 mg. %	10.6-17.5 mg. %
Creatinin	1.2-1.8 mg. %	1.3-1.7 mg. %
Icteric Index	4-5 units	4-5.2 units
Van den Bergh Test	Negative	Negative
Cephalin	Negative	Negative-1 plus
Phosphorus	2.4-4.2 mg. %	2.4-5 mg. %
Phosphatase	1.8-7.7 Bodansky units	2.9-12 Bodansky units
Total Cholesterol	117-193 mg. %	140-195 mg. %
Free Cholesterol	17-45 mg. %	41-60 mg. %
Cholesterol Esters	88-156 mg. %	90-154 mg. %
Total Serum Proteins	6.9-7.9 Gm. %	6.7-8.3 Gm. %
Globulin	2.1-3.4 Gm. %	1.7-3.6 Gm. %
Albumin	3.9-5.8 Gm. %	4-6.8 Gm. %
A/G Ratio	1.1-2.8	1.1-3.2
Urine	Negative; rare hyaline casts	Negative; occasional hyaline casts

As far as could be determined, there were no harmful effects from the tests made. However, in three of the patients the cephalin flocculation test became one plus and a few hyaline casts appeared in the urine.

In view of this, the urine of ten children was examined before and then checked twenty-four hours after the injection of 0.02 mg. (0.2 c.c. of 100 μg per cubic centimeter) of hyaluronidase given on three successive days. The results are listed in Table II.

TABLE II. EFFECT OF HYALURONIDASE ON URINE

CASES	BEFORE INJECTION	AFTER FIRST INJECTION	AFTER SECOND INJECTION	AFTER THIRD INJECTION
1	Neg.	Alb.	Neg.	Neg.
2	Neg.	Neg.	Neg.	Neg.
3	Alb.	Neg.	Neg.	Neg.
4	Alb.	Neg.	Neg.	Neg.
5	Neg.	Neg.	Neg.	Neg.
6	Neg.	Alb.	Neg.	Neg.
7	Alb.	Alb.	Alb.	Neg.
8	Alb.	Alb.	Neg.	Neg.
9	Alb.	Neg.	Neg.	Alb.
10	Neg.	Neg.	Neg.	Neg.

It can be seen from this limited study that hyaluronidase had no harmful effects on the kidney, according to urine examinations.

Cephalin flocculation studies also were done on six children before and after the injection of 0.02 mg. of hyaluronidase. Again the findings revealed that there were no harmful effects.

Various dilutions of the drug were tested to see what variations there were and to decide which dilution would best suit the purpose for fluid administration and skin testing.

Two groups of medical students and one group of normal infants were tested by intradermal injections of 0.2 c.c. of various concentrations of hyaluronidase, and the absorption time determined. The results are shown in Table III.

TABLE III. HYALURONIDASE DILUTIONS PER CUBIC CENTIMETER

NUMBER OF PERSONS	1 MG. (TIME IN SEC.)	1/10 MG. (TIME IN SEC.)	1/100 MG. (TIME IN MIN.)	1/1000 MG. (TIME IN MIN.)	1/10.000 MG. (TIME IN MIN.)	NORMAL SALINE (TIME IN MIN.)	M/6 LACTATE (TIME IN MIN.)
5 Adults	36	88	8	21	25	59	65
7 Adults	32	84	7.5	14.5	23.5	60	63
5 Children	29	92	7.3				

It can be noted that as the solution was diluted, the time required for absorption of the fluid increased proportionately. It was felt that the 1/100 mg. of hyaluronidase per cubic centimeter would be the best dilution to use for skin testing from the standpoint of accuracy and safety because:

1. The variation between the groups tested with this dilution was minimal.
2. Fluid absorption was not too rapid so that better control could be maintained, and yet it was not slow enough to delay the progress of the tests too long.
3. Sensitivity was just as marked with this dilution as with greater concentrations, and therefore it would be safer as well as more economical.

Having decided on the strength of solutions to use and since hyaluronidase had no discernible harmful effects on any of the individuals, a study of sensitivity was undertaken.

One hundred and eight skin tests were done using 0.002 mg. (2 μg) per dose. The procedure followed was the intradermal administration on the forearm of 0.2 c.c. of a solution containing 10 μg Hyaluronidase per cubic centimeter. Of seventy-nine children, seven had positive reactions, or 8.9 per cent. Of twenty-nine adults, three had positive reactions, or 10 per cent. In the total group, there were ten positives or a 9.3 per cent incidence of reaction.

A positive reaction consisted of a wheal with pseudopods appearing within five minutes, persisting for twenty to thirty minutes and associated with itching.

Since the hyaluronidase still contained impurities, a more purified extract was obtained and tried on two of the positive reactors. The reactions remained positive. Thus, the percentage of positive reactions just given would hold until a more purified product can be obtained.

The degree of pain associated with clysis, both with and without hyaluronidase, was next studied. Clyses of 70 c.c. were given into the anterior aspect of the mid-thigh of each of two volunteers. The needles were inserted into what appeared to be identical areas. Then 20 c.c. of a solution of lug of hyaluronidase per cubic centimeter in normal saline were given on one side and 20 c.c. of normal saline on the other. Then an additional 50 c.c. of normal saline were given on each side.

Dull pain was experienced on both sides, but it disappeared more rapidly on the hyaluronidase side, where it lasted two minutes and the swelling was gone in eight minutes. On the other side, there was prolonged dull pain and swelling, which lasted one hour.

In addition, the urinary output was checked on the day of the test and compared with that of the day before and after. No definite consistent alteration in output could be detected.

Studies relative to the effect of this product when added to adrenalin, penicillin, procaine, and streptomycin were done, and in each case the hyaluronidase facilitated absorption, as illustrated in Table IV.

TABLE IV. EFFECT OF HYALURONIDASE ON ABSORPTION OF MEDICATIONS

SOLUTION	TIME IN MINUTES NO. OF PATIENTS 5	 11
Hyaluronidase in Saline	5,9	5-11
Streptomycin and Hyaluronidase	5-9	
Streptomycin in Saline	50-70	
Adrenalin in Saline	40-65	
Adrenalin and Hyaluronidase		8-17
Procaine and Hyaluronidase		6-12
Penicillin and Hyaluronidase		5-10

Following these studies, hyaluronidase was tested on patients with various conditions such as acute infections with elevated temperatures, allergies, and rheumatic fever. To these patients, 0.2 c.c. of 100 μg per cubic centimeter was given intradermally and the time of absorption noted. The results are given in Table V.

TABLE V. EFFECT OF HYALURONIDASE IN SALINE ON VARIOUS CONDITIONS

CONDITION	NUMBER OF PATIENTS	NUMBER OF MINUTES FOR ABSORPTION
Elevated Temperature	10	4-8
Allergies	10	5-9
Rheumatic Fever	6	5-11

As can be seen from Table V, the rate of absorption was fairly equal in all types of conditions. The tests were repeated on the patients with elevated temperature when their temperature was normal, and no difference was noted.

Having decided that the drug was effective and safe if sensitivity were ruled out, it was then used on the following ten patients:

CASE REPORTS

CASE 1.—K. D. was a 2½-year-old white girl who had been operated on for ruptured appendix with peritonitis. Postoperatively she was given 0.02 mg. (20 μg) hyaluronidase in the lateral aspect of each thigh, followed by 1,500 c.c. of normal saline. This was repeated for three days without changing the site of the needle. Through a misunderstanding, the needle was removed for four hours on the fourth day but later replaced in the same area and a clysis of 500 c.c. saline given on the fourth day and 1,500 c.c. of Ringer's solution and 2½ per cent glucose on the fifth day. The absorption was exceptionally good, and there was no evidence of any tissue reaction.

CASE 2.—A. H. was a 7-month-old infant with miliary tuberculosis, who was given 2,500 c.c. of 5 per cent glucose in saline over a period of five days, preceded by 20 μg of hyaluronidase (0.2 c.c. of 100 μg per cubic centimeter) in each thigh. The needles were left in the same place during this period, but after the third day there was inflammation of the tissue about the needle at the site of its insertion.

CASE 3.—M. C. was a 21-month-old female infant admitted for pneumonia with associated vomiting, diarrhea, and dehydration. She was given 200 c.c. of normal saline by clysis on two consecutive days, each one preceded by 20 μg (0.2 c.c. of 100 μg per cubic centimeter) of hyaluronidase. Absorption was satisfactory, and no discomfort to the patient was noted.

CASE 4.—F. B. was a 14-week-old infant who developed diarrhea. She was given 500 c.c. of 5 per cent glucose in saline into an area infiltrated with 20 μg of hyaluronidase in the lateral aspect of the leg. This was repeated the next day in the same area without the use of additional hyaluronidase, and absorption was still satisfactory.

CASE 5.*—R. T. was a 3-week-old infant with pyloric stenosis. Three hundred cubic centimeters of 2½ per cent glucose in Hartman's solution were given on three successive days in the same area, preceded by 0.3 c.c. of 100 μg per cubic centimeter of hyaluronidase. The rate of flow was adjusted to 8 to 12 drops per minute. On the first day, the solution ran for six and one-fourth hours, on the second day for four and three-fourths hours, and on the third day for five and one-fourth hours. At no time was there any elevation of the skin of the thighs at the site of the clysis.

CASE 6.*—M. B. was a newborn premature infant weighing 2½ pounds. One-tenth cubic centimeter of 100 μg per cubic centimeter of hyaluronidase in 40 c.c. of 2½ per cent glucose in Hartman's solution was used on five occasions with steady absorption each time.

CASE 7.*—A. V. was a child with acute otitis media and a temperature of 104° F. Combined sulfadiazine and sulfamerazine were given subcutaneously and as the child was not taking fluids, a clysis of 500 c.c. of 2½ per cent glucose in Hartman's solution with 0.5 c.c. of 100 μg per cubic centimeter of hyaluronidase was given. The clysis was completed in six hours. Only slight elevation of the skin of the thigh was noted.

CASE 8.—J. W. was a 6-week-old infant with diarrhea secondary to otitis media. He was given 200 c.c. of 5 per cent glucose in saline preceded by 20 μg of hyaluronidase. The clysis was continued for five hours with no swelling or discomfort.

CASE 9.—S. C. was a 33-year-old woman who had had a hysterectomy. She was given a clysis of 1,000 c.c. of 5 per cent glucose at the rate of 100 drops per minute, and it was completed in three hours. Twenty micrograms of hyaluronidase (0.2 c.c. of 100 μg per cubic centimeter) were given at the start of the clysis. There was slight swelling of the tissues after the clysis, but it was diffuse and not indurated.

CASE 10.—J. P. was a 33-year-old woman who had been operated on for a ruptured appendix. She was given 1,000 c.c. of 5 per cent glucose in water, preceded by 20 μg of hyaluronidase. The clysis was completed in two and two-thirds hours, and there was slight swelling but no induration in the area.

DISCUSSION

Hyaluronidase was first described by Duran-Reynals[5] and McClean[6] as a spreading factor, but its identity as a mucolytic enzyme and its presence in all sources of the spreading factor was established by Chain and Duthie[4] and confirmed by several others.[7-9]

*Patients studied at Flower-Fifth Avenue Hospitals.

This enzyme has been obtained from numerous sources, such as bacteria,[4, 10-14] leech extracts,[4, 15] bee, snake, and spider venoms,[4, 16] spermatozoa,[17-19] and mammalian testes.[4, 20]

Its role in infection[4] and fertilization[20-22] has been formulated, and more recently its role in fluid administration has been studied. In the present paper, the enzyme was studied from the latter point of view.

Enough of the hyaluronidase was given to several individuals to equal the amount that would be needed for the average clysis (20 μg), and no harmful effects could be noted. In ten cases the hyaluronidase was repeated on three consecutive days, and no harmful effects on the urine were observed.

However, in testing skin sensitivity, 9.3 per cent of those tested had positive reactions, which suggests the advisability of skin testing each individual prior to administration of the enzyme. In fairness to the product, it must be added that it has not been completely purified, and perhaps the percentage of sensitivity can be reduced as more impurities are removed.

It was also noted that the addition of hyaluronidase to saline gave almost identical absorption times for all patients (healthy or ill, regardless), the difference being almost negligible, whereas in the Aldrich and McClure "saline test"[23] the rates of absorption were much more rapid in infectious diseases. This suggests[4] that during illness there may be an increase of hyaluronidase formation by bacteria or possibly a decrease in hyaluronic acid formation in the tissue which increases the absorption of the saline.

The most important observation of all was that absorption of various types of solutions, such as saline, glucose in saline, Hartman's solution, Ringer's solution, penicillin, streptomycin, adrenalin, and procaine, was facilitated in every case.

In two of the patients clyses were run for five days, the needles remaining in the same area. It was noted that the tissue about the needle became inflamed after the third day; therefore it would be wise to change the site of the needle after that time.

Absorption was facilitated and pain diminished in every case. No consistent alterations in body physiology were detected.

SUMMARY AND CONCLUSION

1. Hyaluronidase had no harmful effect on any of the patients studied, although a positive intradermal skin test was obtained in 9.3 per cent.

2. The extent and duration of the pain and swelling associated with clysis were greatly reduced by use of the enzyme.

3. No alteration in body physiology was detected.

4. It greatly facilitated absorption of all solutions used.

5. The rate of absorption was practically identical for all patients, whether ill or not.

6. Continuous clysis for at least five days could be given, with the needle shifted after the third day.

7. It must be concluded that hyaluronidase proved of great value in the treatment of dehydrated infants. However, it would be of even greater value

were the product further purified so as to decrease the sensitivity factor. It is felt that hyaluronidase should be added to the medical armamentarium as a means of saving many children's lives.

Appreciation is gratefully expressed for the valuable assistance rendered in this study by Jack Hennessen and other members of the Senior Group of the New York Medical College and Flower-Fifth Avenue Hospitals.

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THE ORAL AND SUBCUTANEOUS ADMINISTRATION OF p-AMINOMETHYLBENZENESULFONAMIDE (SULFAMYLON)

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THE unique properties of *p*-aminomethylbenzenesulfonamide (*p*-(α-amino) toluenesulfonamide, homosulfanilamide, Marfanil, Sulfamylon*) have elicited considerable interest in its potentialities as a chemotherapeutic agent. It differs widely from other sulfonamides in certain important characteristics. In contrast to these compounds, Sulfamylon is freely soluble in water, to the extent of 50 Gm. per 100 ml. at 25° C. Its antibacterial action is in no way antagonized by either p-aminobenzoic acid or p-aminomethylbenzoic acid, and thus an entirely different mechanism of action is suggested.[1, 2] Although Sulfamylon is effective against most organisms inhibited by other sulfonamides, it is, in addition, highly effective in vitro against a number of anaerobic bacteria, particularly clostridia.[3]

Sulfamylon was first utilized in Germany in the local treatment of various wound infections[4] and subsequently specifically in the management of gas gangrene.[5-8] More recently it has been applied to the systemic therapy of certain bacterial diseases, such as urinary tract infections, especially those resistant to other antibacterial agents.[9] Recently a method for the quantitative determination of Sulfamylon in blood[10] has been developed, making possible the present study on certain aspects of the pharmacology of this drug.

PLAN OF STUDY

The subjects were patients on the medical wards of the St. Louis Children's Hospital, who were for the most part convalescents free of gastrointestinal and renal disease. However, one patient with pyelonephritis and another with typhoid were included. The ages ranged from 7 months to 14 years.

Sulfamylon hydrochloride was given orally in the form of either 0.5 Gm. tablets or a 15 or 20 per cent solution in diluted (aqueous) syrup of cherry. A one per cent solution for subcutaneous administration was prepared by dilution of a Seitz-filtered 20 per cent aqueous solution of the hydrochloride with the appropriate volume of lactate Ringer's solution. At suitable intervals after single doses of the drug, blood samples were obtained and the concentration of Sulfamylon in the serum determined by the method previously described.[10]

From the Department of Pediatrics, Washington University School of Medicine, and the St. Louis Children's Hospital.

Much of this study was made possible through the aid of the Children's Research Foundation.

*Sulfamylon is the trade name of the product made by the Winthrop Chemical Company, New York, N. Y., which kindly supplied the material used in this study. For convenience, the name Sulfamylon will be used in place of p-aminomethylbenzenesulfonamide throughout this article.

All patients were observed closely for toxic manifestations, and all patients capable of reporting were questioned about toxic symptoms. Routine urinalyses and blood counts were carried out both before and after administration of the drug.

ORAL ADMINISTRATION

Included as subjects in this group were both infants and older children. A single dose of Sulfamylon hydrochloride was given to each subject, and the

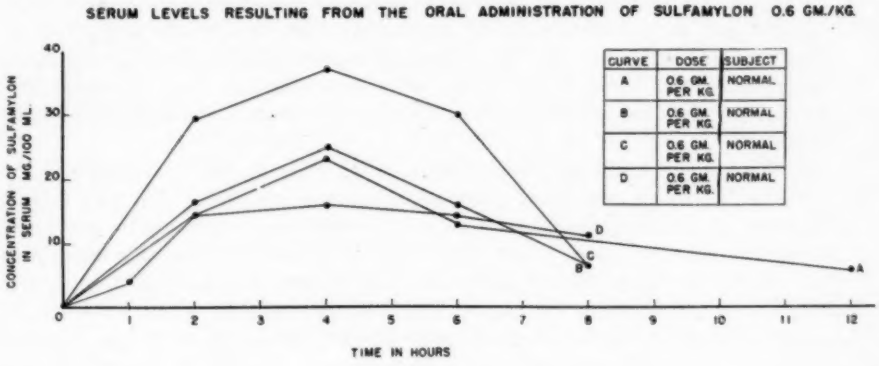
SERUM LEVELS RESULTING FROM THE ORAL ADMINISTRATION OF SULFAMYLON 0.6 GM./KG.
CONCENTRATION OF SULFAMYLON IN SERUM MG./100 ML.
TIME IN HOURS
CURVE | DOSE | SUBJECT
A | 0.6 GM. PER KG. | NORMAL
B | 0.6 GM. PER KG. | NORMAL
C | 0.6 GM. PER KG. | NORMAL
D | 0.6 GM. PER KG. | NORMAL

Fig. 1.

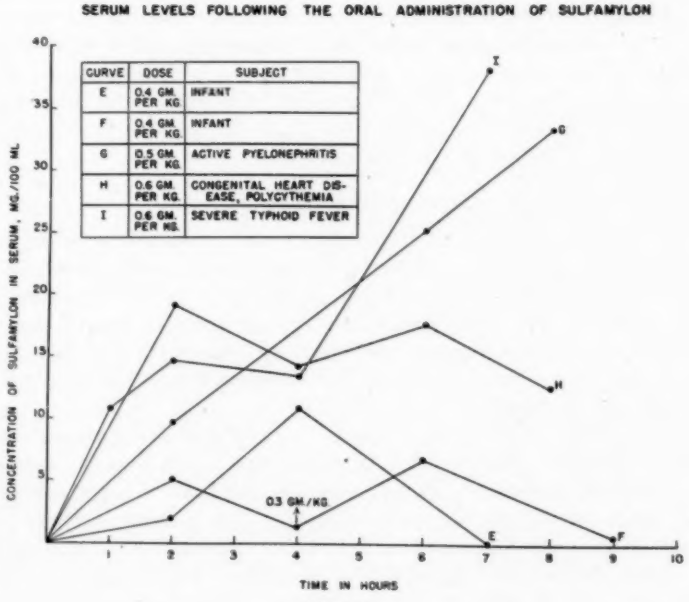
SERUM LEVELS FOLLOWING THE ORAL ADMINISTRATION OF SULFAMYLON
CONCENTRATION OF SULFAMYLON IN SERUM, MG./100 ML.
TIME IN HOURS
0.3 GM./KG.
CURVE | DOSE | SUBJECT
E | 0.4 GM. PER KG. | INFANT
F | 0.4 GM. PER KG. | INFANT
G | 0.5 GM. PER KG. | ACTIVE PYELONEPHRITIS
H | 0.6 GM. PER KG. | CONGENITAL HEART DISEASE, POLYCYTHEMIA
I | 0.6 GM. PER KG. | SEVERE TYPHOID FEVER

Fig. 2.

serum concentration of the drug was followed, usually by determination at two-hour intervals. The dosage ranged from 0.4 to 0.6 Gm. per kilogram of body weight. The observed data are presented in Figs. 1 and 2.

The most typical pattern is seen in the curves of Fig. 1. With a dosage of 0.6 Gm. per kilogram of body weight, there is a rise of the blood level to a peak approximately four hours after administration with subsequent rapid fall, so that by eight hours the serum level has returned to the vicinity of 10 mg. per 100 ml. or lower. Twenty-four hours after a single dose of 0.6 Gm. per kilogram of body weight there is no appreciable Sulfamylon remaining in the blood. Thus, fairly rapid absorption but rapid removal by excretion or destruction is indicated, and comparatively high dosage is needed to achieve the blood levels reported here. While dosage will obviously affect the drug concentrations obtained, individual differences in absorption evidently also effect considerable variation.

Comparison of all the curves presented in Figs. 1 and 2 demonstrates the wide variability in individual response to a single oral dose. The two infants reported in Curves E and F and two others studied with only one or two determinations achieved much lower blood levels than did children over 2 years of age on similar dosage, failing to attain serum concentrations higher than 10 mg. per 100 ml. at any time. Evidently the absorption of Sulfamylon from the immature digestive tract is relatively poor; similar phenomena have been observed upon oral administration of other sulfonamides.[11] In Fig. 2, Curve G's persistent rise can be explained on the basis of impaired excretion of the drug in the presence of pyelonephritis, while Curve I's delayed peak may be related to delayed absorption and impairment of renal function in a case of severe typhoid fever with cardiac failure. However, it is obvious that a wide variation in individual response may exist in the absence of any evident pathologic change to explain it. There are evidently marked individual differences in the ease with which Sulfamylon is absorbed from the alimentary canal, analogous to those observed in the case of other sulfonamides.

SUBCUTANEOUS ADMINISTRATION

All subjects receiving Sulfamylon by the subcutaneous route were convalescent patients, less than 2 years of age, without gastrointestinal or renal disease. A single infusion of one per cent Sulfamylon hydrochloride in lactate Ringer's solution was given, and serum levels of the drug were followed at one- or two-hour intervals. Dosage was either 0.5 Gm. or 0.6 Gm. per kilogram of body weight, except for one 0.3 Gm. per kilogram dose. The observed data are presented in Figs. 3 and 4.

Examination of these data reveals that all six curves adhere closely to a consistent pattern. The rise of Sulfamylon concentration in the serum is rapid but varies with the rate of infusion, and the peak level in every case comes very shortly after the end of the hypodermoclysis. This indicates that the absorption of Sulfamylon from subcutaneous fluid is very rapid. There is a rapid fall of drug concentration after the peak level is reached, so that again the blood level is generally near or below 10 mg. per 100 ml. within four hours after the peak.

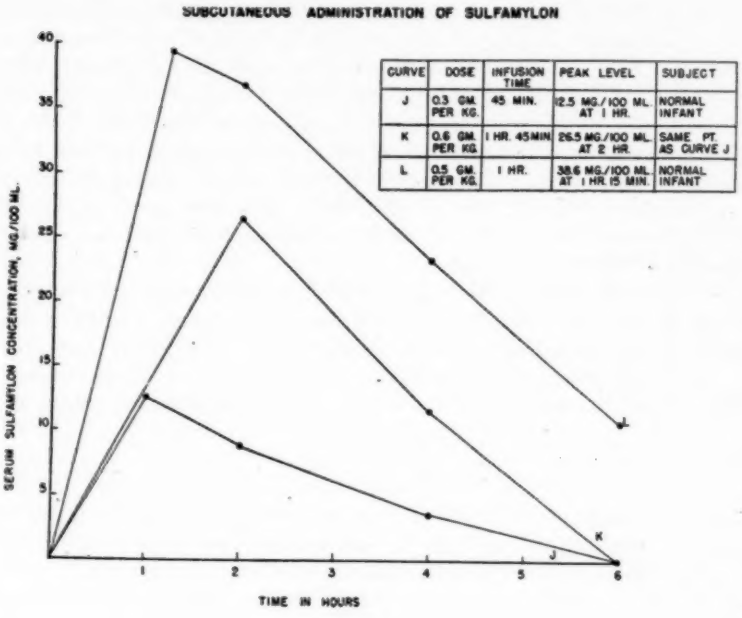
SUBCUTANEOUS ADMINISTRATION OF SULFAMYLON
SERUM SULFAMYLON CONCENTRATION, MG./100 ML.
TIME IN HOURS
CURVE | DOSE | INFUSION TIME | PEAK LEVEL | SUBJECT
J | 0.3 GM. PER KG. | 45 MIN. | 42.5 MG./100 ML. AT 1 HR. | NORMAL INFANT
K | 0.6 GM. PER KG. | 1 HR. 45 MIN. | 26.5 MG./100 ML. AT 2 HR. | SAME PT. AS CURVE J
L | 0.5 GM. PER KG. | 1 HR. | 38.6 MG./100 ML. AT 1 HR. 15 MIN. | NORMAL INFANT

Fig. 3.

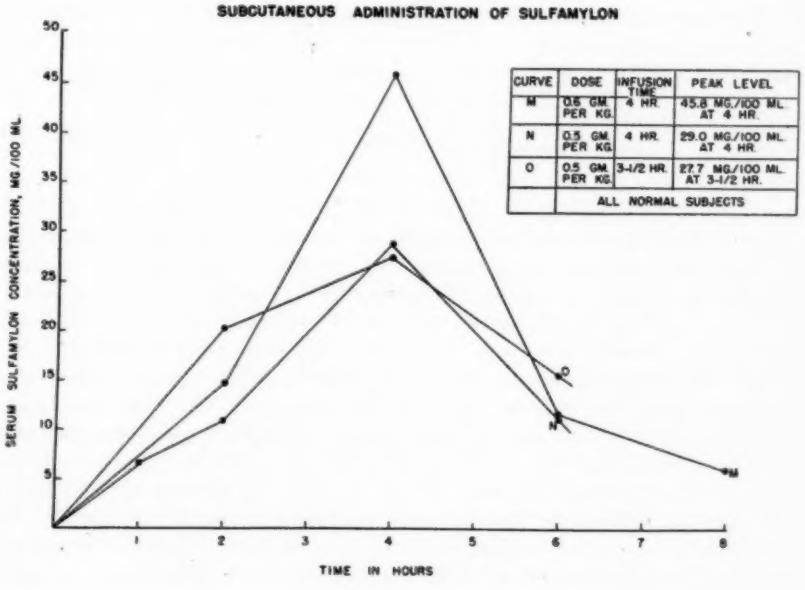
SUBCUTANEOUS ADMINISTRATION OF SULFAMYLON
SERUM SULFAMYLON CONCENTRATION, MG./100 ML.
TIME IN HOURS
CURVE | DOSE | INFUSION TIME | PEAK LEVEL
M | 0.5 GM. PER KG. | 4 HR. | 45.8 MG./100 ML. AT 4 HR.
N | 0.5 GM. PER KG. | 4 HR. | 29.0 MG./100 ML. AT 4 HR.
O | 0.5 GM. PER KG. | 3-1/2 HR. | 27.7 MG./100 ML. AT 3-1/2 HR.
ALL NORMAL SUBJECTS

Fig. 4.

On the whole, blood levels obtained by the subcutaneous route are higher than those reached after oral administration of the same amount of Sulfamylon. In addition, the comparative uniformity of the response in different individuals receiving the drug subcutaneously is striking, and direct correlation of blood levels attained with the dosage received is observed, although there is some degree of individual variation. This adherence of curves obtained from subcutaneous administration to a nearly uniform pattern, as contrasted with the marked heterogeneity of the oral administration curves, confirms the idea that the variability shown in Figs. 1 and 2 is primarily in absorption, rather than excretion, in different individuals.

Upon comparison of the results of subcutaneous and oral administration it becomes evident that the subcutaneous route is indicated in children less than 2 years of age and offers a marked advantage in reproducibility in patients of any age. It obviously also presents a valuable method of administration in patients who are nauseated or vomiting, have gastrointestinal disease, or are severely ill.

NOTES ON MAINTENANCE OF THERAPEUTIC LEVELS

It may be inferred from the data presented that comparatively high dosage, similar to that utilized in these studies, repeated at fairly frequent intervals, is necessary to maintain serum levels at or above 10 mg. per 100 ml. Since clinical data indicating the approximate Sulfamylon levels necessary for effective treatment of various bacterial diseases have not yet been reported in the literature, no attempt will be made at present to recommend specific dosage schedules.

Certain additional observations are pertinent to the problem of maintaining therapeutic concentrations. Absorption after oral administration is variable but often quite adequate in patients above 2 years of age, while in infants it is very ineffective. More rapid attainment of a given blood level is obtained by subcutaneous administration, and in general it gives more reproducible results, besides being indicated in treating infants or patients unable to take or retain Sulfamylon orally or absorb it well.

TOXICITY

All patients who received Sulfamylon hydrochloride orally and were capable of reporting their symptoms complained of nausea and headache, appearing shortly after the drug was taken. Three out of eleven subjects observed some dizziness, and two complained of mild mental confusion and slight dissociation. Two of the patients were sufficiently nauseated to vomit their first dose of the drug. All subjects receiving subcutaneous Sulfamylon were too young to communicate any untoward symptoms. Close observation of all patients receiving the single large oral or subcutaneous doses revealed no clinical signs of toxicity.

In view of the fact that the pH of a one per cent aqueous solution of Sulfamylon hydrochloride is 5.5, the drug was administered subcutaneously as one per cent Sulfamylon hydrochloride in lactate Ringer's solution; the pH of this preparation was 6.5. No local irritation or other signs of reaction at the site of injection were observed, and no pyrogenic or other systemic reactions

occurred. A 2 per cent solution of Sulfamylon in lactate Ringer's solution is equally free from side effects and provides a more convenient volume for infusion.

Sulfamylon hydrochloride is the salt of a strong acid and a weak base; hence its solutions are acidic. In the case of one patient maintained at high levels of Sulfamylon for twenty-three hours, acidosis developed. This girl, who was suffering from severe typhoid fever, received the following dosage of Sulfamylon hydrochloride: 0.6 Gm. per kilogram of body weight orally at 9:30 A.M.; 0.6 Gm. per kilogram orally at 3:30 P.M.; 0.55 Gm. per kilogram subcutaneously, as one per cent in lactate Ringer's solution, starting at 4:50 P.M.; 0.6 Gm. per kilogram orally at 8 P.M., 12 midnight, 4 A.M., and 8 A.M.; after this the drug was discontinued because of indications of resistance of the organism to Sulfamylon in vitro. At 4:30 P.M. the serum Sulfamylon level was 38 mg. per 100 ml., and at 8 A.M. it was 111 mg. per 100 ml. Hence we may assume that the serum level was above 30 mg. per 100 ml. for at least sixteen hours. At 8 A.M. the serum carbon dioxide content was found to be reduced to 29 volumes per cent. Upon simple discontinuance of the drug, without administration of additional base, acidosis was relieved spontaneously within eight hours, despite the massive concentration of Sulfamylon present at 8 A.M.

Routine urinalyses and blood counts were carried out upon all patients before and after administration of Sulfamylon. No abnormalities were shown in either. In particular, there were absolutely no laboratory or clinical signs of renal damage despite the high single doses. The patient with severe typhoid fever mentioned previously subsequently died and came to autopsy. There were no signs of toxic effects in the kidney, and no lesions in any part of the body that could be attributed to the drug. This is especially significant in view of the exceedingly high concentration of Sulfamylon maintained in this patient's blood. Additional evidence of the absence of renal damage was found in the fact that twenty-four hours after the serum level was found to be 111 mg. per 100 ml., it had dropped to less than 2 mg. per 100 ml.

SUMMARY

Single doses of Sulfamylon (hydrochloride) were administered to subjects and the blood levels followed at suitable intervals. Marked individual variations in absorption are evident after oral administration, with absorption apparently very poor in infants, while the data from subcutaneous administration present a relatively uniform picture. Sulfamylon is evidently excreted rapidly, and comparatively high dosage is required to attain appreciable concentrations in the blood serum.

Immediate toxic symptoms of headache and nausea were reported by all patients taking Sulfamylon orally, while dizziness and mental confusion were experienced by three. No local or systemic reactions were produced by the subcutaneous infusion of one per cent Sulfamylon hydrochloride in lactate Ringer's solution. No evidence of renal damage or hematopoietic depression was found either in routine urinalyses and blood counts on all patients or on post-mortem examination of one patient receiving very intensive Sulfamylon therapy for one day.

Grateful acknowledgment is made to Dr. Alexis F. Hartmann for advice and suggestions during the course of this work and in the preparation of this paper.

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GENERALIZED VACCINIA

A Study of Fifteen Cases

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DURING the New York City smallpox outbreak of March, 1947, a well-known radio commentator made the following statement: "During this period there have been more deaths resulting from complications of vaccination than there have been deaths from smallpox." This true though very inept remark undoubtedly was misinterpreted by many listeners to be a condemnation of smallpox vaccination as a dangerous procedure.

The more pertinent facts that might have been revealed by the commentator include:

1. The incidence of smallpox in the United States has been reduced as a result of an improved vaccination program from an average annual rate of 40,000 cases twenty years ago[1] to an average of less than 500 cases per annum during the years 1942 to 1947.[2]

2. By the prompt vaccination of more than six million individuals[3] at the time of the New York outbreak, a potential smallpox epidemic was limited to a total of fourteen cases.[4]

3. Smallpox vaccination with fully potent vaccine, performed according to any one of the accepted methods, is with rare exceptions, a safe procedure.

It is proposed that if the severe vaccination complications can be further reduced to an absolute minimum, at least one of the obstacles impeding a nation-wide compulsory vaccination program will have been removed.

Our study was made with the purpose of recalling to the attention of the general practitioner and the pediatrician the severe vaccination complication commonly known as generalized vaccinia. It is our belief that by careful attention of the vaccinating physician to a few prophylactic measures, the incidence of this condition will be markedly decreased.

In a recent report on certain aspects of the New York smallpox outbreak and subsequent mass vaccination, Muckenfuss[3] stated that thirty-six cases of generalized vaccinia are known to have occurred. Twenty-two of the persons so affected had not themselves been vaccinated. Our series consists of fifteen of these thirty-six individuals who manifested generalized vaccinial lesions. These patients were admitted to the Willard Parker Hospital for Contagious Diseases in April and May, 1947.

The patients with generalized vaccinia whom we observed were acutely and distressingly ill. This was especially true of the infants and young children in whom multiple vaccinial lesions were superimposed upon an atopic eczema. Rather complete clinical and laboratory studies were made on each of the fifteen

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patients, but since to report every case in detail would be repetitious, only four are described. These case reports, together with the data in Table I and the subsequent discussion, will present the outstanding characteristics of generalized vaccinia as observed in this series.

CASE REPORTS

CASE 1.—This was a Negro male infant, 3 months of age, admitted to the hospital May 7, 1947. The history indicated that the child had suffered from eczema of the face and scalp since the age of one month.

According to the parent's statement, the sequence of events immediately preceding the child's admission to the hospital was as follows: The mother was vaccinated against smallpox April 14, with a resulting primary vaccinia which reached its height on April 23. Ten days later the infant (who had not been vaccinated against smallpox) developed pustular vesicles on the face. Shortly afterward similar lesions appeared on the scalp, upper extremities, trunk, and legs, and four days later the infant was so ill as to necessitate hospital care.

Fig. 1.—Patient in Case 1. Photograph taken on the fifth day of illness.

When this infant was admitted to the hospital, he was acutely ill and semicomatose. The temperature was 105° F., the pulse and respirations extremely rapid. Masses of confluent crusted lesions, from some of which pus oozed, were on the face. The right eyelid was closed by extensive involvement of that area, but there was no corneal lesion. Lesions on the scalp, anterior trunk, and extremities were present, though more discrete and of varying stages. One pustule was present on the right palm, but there was no involvement of the mucous membranes. The typical individual lesion was a slightly raised, flat pustule, 5 to 7 mm. in diameter, at first umbilicated, later crusted.

High fever and extreme prostration continued for the first four days of hospitalization, with daily elevations of temperature to 104° and 105° F. Thereafter the temperature fell by lysis and remained normal after the tenth hospital day. By the end of the first week of hospitalization (eleven days after onset) the individual skin lesions were desquamating and forming new crusts. The areas where lesions had previously coalesced on the face became raw and weeping. After eleven days in the hospital the lesions on the

body were fairly well cleared, and the skin of the face and extremities was assuming an eczemoid character. The lesions of the right eyelid had subsided, and the eye itself was normal.

Routine urinalysis was negative. Admission cultures of the lesions were positive for *Staphylococcus aureus* and *Bacillus proteus*. Hemoglobin was 63 per cent, with a red blood cell count of 4 million. The white blood cell count was 13,100, with neutrophiles 56 per cent, lymphocytes 35 per cent, myelocytes 2 per cent, metamyelocytes 2 per cent, monocytes 2 per cent, eosinophiles 3 per cent. The Paul test was positive, and vaccinia virus was recovered on chorio-allantoic culture.

Treatment consisted of penicillin, 10,000 units given intramuscularly every three hours, prevention of self-traumatization by the combination of methods to be described under *Treatment*, penicillin ointment applied locally to the lesions, and hot compresses used for the palpebral edema. A soybean milk substitute was given, and known or suspected allergens were eliminated from the diet.

On subsidence of the acute illness and of the vaccinia lesions, local treatment was instituted for the underlying eczema, and on the thirtieth hospital day the patient was discharged. At that time the face and upper extremities were moderately scarred. Follow-up two weeks after discharge revealed depigmentation without pitting of the areas previously involved by the vaccinia lesions.

CASE 2.—The patient was an 8-month-old white male infant admitted to Willard Parker Hospital May 16, 1947, because of high fever and a generalized pustular eruption. The history included typical infantile eczema with onset at the age of 3 weeks followed by alternate periods of improvement and exacerbation.

When the infant was 6 months old the mother inquired of the family doctor concerning smallpox vaccination and was advised against the procedure because of the presence of infantile eczema. Consequently the patient had never been vaccinated. However, approximately two weeks before the admission date both parents were vaccinated and developed what apparently were accelerated reactions.

On examination of the infant on May 11, there were noted by the family doctor confluent vesicular lesions on the left side of the face. In the four days preceding admission these lesions extended to involve all parts of the body except the posterior aspect of the trunk, the genitalia, the soles of the feet, and the right palm.

Examination on admission to the hospital revealed a desperately ill male infant with a temperature of 103° F., and scratching the involved areas of skin with both hands and feet. An umbilicated pustular eruption was present, the lesions being confluent in the left cervical region and left cheek and discrete on the right side of the face, the anterior surface of the trunk, and the extremities. Three lesions were noted on the left palm.

The typical discrete lesion was firm, pustular, and umbilicated, measuring about 0.5 cm. in diameter. Some lesions were mounted on an erythematous base. Not all lesions had developed this characteristic umbilicated appearance, while others had advanced to the crusting stage. Areas of excoriation in which the skin had apparently been completely denuded by scratching were present on the arms, legs, and chest.

There was noted a generalized lymphadenopathy with most marked enlargement of the axillary and inguinal glands. The largest of these glands measured about 2 cm. in diameter. Skin turgor on admission was poor.

The red cell count was 4.34 million, and the hemoglobin was 13 Gm. or 90 per cent of normal. The total white count was 12,800, with 85 per cent polymorphonuclear cells and 15 per cent lymphocytes. Total serum protein was 5.1 Gm. per cent, of which albumin constituted 3.2 Gm. per cent and globulin 1.9 Gm. per cent. The Paul test was negative. Material from the lesions showed a type of growth characteristic of vaccinia virus on the chorio-allantoic culture.

The infant's temperature rose to 103° F. on the second and third hospital days. The extremities became spastic, nystagmus developed, and the skin turgor was only slightly improved. The skin lesions were observed to progress rather rapidly through the umbilicated stage to the crusted stage.

A soybean formula was taken fairly well by mouth, while plasma was given intravenously and normal saline was given by clysis. Aspirin and tepid sponges on uninvolved surfaces were used in an attempt to control fever. Penicillin was administered intramuscularly, and penicillin ointment was applied locally.

The infant failed to respond to treatment. Fever, spasticity, and nystagmus persisted, and death occurred on the fourth hospital day.

Post-mortem examination revealed an extensive crusting pustular eruption involving particularly the cheeks, forehead, arms, and legs, with a few lesions noted on the left palm. Microscopic examination of a typical skin lesion revealed a superficial flat vesicle covered with coagulated epithelium and filled with some cellular debris, along with polymorphonuclear cells and groups of cocci. Areas of mononuclear infiltration were noted in the subjacent corium. The brain appeared quite pale, and the meninges were slightly edematous. The weight of the brain was 830 Gm., and sectioning showed no significant congestion. Microscopic examination of various parts of the brain showed mononuclear infiltration of the walls of numerous small veins in the white matter and also in the gray matter. The brain substance showed no cellular infiltration around the affected blood vessels, and there was no appreciable loss of myelin. Section of the lumbar cord showed infiltration of the walls of several small veins in the posterior horns, posterior white column, and in the gray commissure.

The anatomical diagnosis was: (1) generalized vaccinia, (2) chronic eczema, (3) encephalomyelitis without loss of myelin.*

CASE 3.—The patient was a 9-month-old Negro male infant who was admitted to Willard Parker Hospital April 27, 1947, because of fever and a skin eruption of twenty-four hours' duration. The infant had infantile eczema at the age of 5 months, but two months before admission there had been a marked improvement in this condition following the substitution for milk of a soybean preparation.

Because of the eczema the infant had not been vaccinated against smallpox. However the parents were vaccinated on April 17, nine days before the onset of the patient's eruption. Both parents developed primary reactions, and shortly thereafter there were noted what were described as pustular lesions about the lobe of the infant's left ear. These lesions were quite pruritic as evidenced by the fact that they were scratched so vigorously as to leave a denuded area.

By the day of admission, pustular lesions had appeared on the right shoulder and extremities. On admission, physical examination revealed an acutely ill, lethargic child. The temperature was 104° F., and the pulse and respirations were correspondingly rapid.

The skin of the face and the left ear was densely covered with umbilicated or crusted raised pustular lesions, some of which were coalescent with denuded weeping patches. The trunk and the extremities, including the dorsum of the hands and feet, were involved by similar lesions, but the mucous membranes and the palms and soles were not involved. Portions of the skin, clear of lesions, were thickened and bore numerous superficial scratch marks. There was a generalized lymphadenopathy with marked involvement of the cervical, posterior auricular, axillary, and inguinal nodes. The remainder of the physical examination was not significant.

Routine urinalysis on admission revealed four-plus albumin. No casts or red cells were observed. The carbon dioxide combining power was 43 volumes per cent. The N.P.N. was 24 mg. per cent. Total serum protein was 6.4 Gm. with an A/G ratio of 1.3 to 1. The hemoglobin was 9 Gm., with a red blood cell count of 4 million. The white blood cell count was 12,000, with a normal differential. A blood culture was negative. The serologic test for syphilis was negative. Inoculation of penicillin-treated material, from the lesion to the chorio-allantoic membrane of embryonated eggs, showed a characteristic

*A detailed discussion of this case and of other cases of encephalitis which occurred in New York during the same period will be made by Dolgopol, Greenberg, and Arnoff at a later date.

growth of the vaccinia virus. The Paul test was unsatisfactory. Bone marrow studies performed on material obtained from sternal puncture were within normal limits.

For seven days after admission there were diurnal rises of temperature ranging between 103.8° and 105.4° F. The temperature returned to normal on the tenth hospital day, but there were subsequent elevations to 102° and 105° F. on the sixteenth and twenty-seventh hospital days, respectively.

The lesions appeared in successive crops over the body, with pustular, weeping, and crusted lesions often all present in close proximity. Pustules appearing subsequent to the first crop were observed to mature more rapidly than the initial lesions. With the return of the temperature to normal, on the tenth hospital day, the lesions began to subside and form innocuous-appearing crusts. By the eighteenth hospital day, there was generalized desquamation of the crusts, leaving a severe pruritic eczema. The albuminuria gradually subsided and was no longer observed after one month. Treatment consisted of parenteral and local penicillin, restraints, and a soybean milk formula. Benadryl failed to give any observable alleviation of itching in this case.

The infant was discharged on the forty-second hospital day, with recommendations for further treatment of the eczema at a dermatology clinic. The degree of scarring of the face on discharge was difficult to evaluate because of the eczema which persisted.

CASE 4.—This patient was a 28-month-old white male infant admitted to the hospital April 27, 1947, following vaccination in the left deltoid region on April 17. There was a history of severe and persistent atopic eczema present since early infancy. Benadryl had been used with some temporary improvement of the eczema. Known allergens included citrus fruits, egg, wheat, and chocolate. The only other pertinent fact obtained from the history was a sensitivity of the father to pollens and dusts.

Three days following vaccination there developed marked pruritis in the left deltoid region, which was scratched vigorously by the patient. Small red papular lesions appeared about the vaccination site, and seven days after vaccination the eruption spread to involve the posterior cervical region. At this stage the child appeared acutely ill, became restless and irritable, and the family doctor administered a sedative along with local antipruritics. Further extension of the lesions followed with involvement of all body surfaces except the palms, soles, and mucous membranes.

Physical examination on admission revealed an acutely ill, though well-nourished and well-developed 28-month-old boy with a temperature of 103° F. Firm pustular umbilicated lesions with an erythematous base were noted on the face, neck, trunk, and extremities. The majority of the lesions were umbilicated or weeping, while some were crusted. A few lesions, though pustular in character, appeared to be topped by small vesicles. The conjunctivae and pharynx were injected, and there was a mucopurulent discharge from the eyes and nose. The cervical and left axillary glands were enlarged.

Routine urinalysis showed a trace of albumin and occasional pus cells. The white blood cell count was 11,000 with 50 per cent polymorphonuclears, 46 per cent lymphocytes, 2 per cent eosinophiles, and 2 per cent metamyelocytes. The characteristic vaccinia virus growth was obtained upon inoculation of material from the lesions on the special chorioallantoic culture medium. The Paul test was unsatisfactory. Examination of the sternal marrow revealed no abnormalities.* The Kline test was positive.

The most marked involvement as noted on the second hospital day was of the arms, the suprascapular and posterior cervical regions, and the popliteal fossae. A few lesions were also noted on the eyelids. At this time the eruption was definitely polymorphous. Some lesions were deep-seated, erythematous papules, some were weeping, umbilicated pustules, and still others were crusted.

Treatment consisted of the use of penicillin intramuscularly and locally, sedation, and aspirin as an antipyretic. Restraint constituted a major problem in this case. The combination of methods found to be most efficacious is described in detail under *Treatment*.

*Bone marrow studies in this series were performed by Dr. Thomas Louis Rider of the Willard Parker Hospital house staff.

Response to therapy was satisfactory, the temperature remaining normal after the ninth hospital day, and the patient was discharged on the fourteenth day of hospitalization.

Follow-up examination three weeks after discharge revealed erythematous scaly areas where the vaccinia lesions had been located. No pitting was observed.

Fig. 2.—Patient in Case 6. Photograph taken three days after admission. Note different stages of lesions on cheek and forehead.

DIAGNOSIS

Incidence.—One seldom sees a series of cases of generalized vaccinia unless a large number of persons have been vaccinated against smallpox. There is, however, some indication that virus of unusual potency may be a factor in producing this condition. The most recent report on generalized vaccinia is from Clark and his associates.[6] They estimate an incidence of one case of generalized vaccinia to 13,390 vaccinations. Ross,[7] on the basis of data accumulated by a number of European authors, suggests the incidence as being one in twenty to forty thousand cases of routine vaccination. It is quite likely, however, that this condition is not as rare as statistics would indicate, as mild attacks probably seldom come under medical observation and even when they do are seldom reported. The statistical frequency of generalized vaccinia may well be decreased, too, by the fact that an occasional case is undoubtedly misdiagnosed as variola, impetigo, or secondarily infected varicella.

In the New York experience, with an estimated six million vaccinations, only thirty-six cases of generalized vaccinia came to light. But inasmuch as twenty-two of these patients had not themselves been vaccinated, and because most patients with generalized vaccinia manifest an underlying chronic dermatosis, it would appear not entirely safe to establish an incidence rate by utilizing only discovered cases of generalized vaccinia as the numerator and the number of persons vaccinated against smallpox as the denominator. Attack rates of

generalized vaccinia appear to depend more upon exposure of persons with eczema to vaccine virus than upon the number of persons vaccinated, and it is not practicable to obtain data of this sort. The fifteen patients whom we studied constitute too small a number to yield any data as to incidence of generalized vaccinia by age, sex, or race. Eleven of the patients were Negro, as against four white patients, while the ratio in New York City of white persons to Negroes is about fourteen to one. However the comparative number of white and Negro eczema patients exposed to vaccine virus is not known. Probably, too, economic circumstances brought a greater proportion of Negro than white patients to the Willard Parker Hospital. There were eleven males and four females, and ages ranged from 13 months to 64 years, with a majority of the cases in infants. (See Table I.) It is suggestive, however, that the predominance of males and infants is similar to the distribution of atopic eczema in the general population.

Eight of the fifteen patients had not themselves been vaccinated against smallpox, but the unvaccinated group had been exposed to recently vaccinated members of their respective families. In less than half of this group was there history of direct contact with the vaccination area of another individual.

It is believed that generalized vaccinia does occur more frequently in individuals exhibiting a primary vaccination reaction. All vaccinated individuals in our series had been vaccinated for the first time.

Period of Incubation.—All information upon which the period of incubation of generalized vaccinia might be calculated was obtained from parents and therefore may not be relied upon with confidence. In seven of our patients vaccinated conventionally, the time from date of the vaccination to the manifestation of the first evidence of multiple vaccinia lesions ranged from one to seven days with a mean of 4.5 days. In the series as a whole, including patients for whom data were obviously unreliable, the range was from one to twenty days, with a mean of eleven days and a median of nine days. Perhaps in cases where the patient was not himself vaccinated, it would be more nearly exact to date exposure as of the day that vaccination in the source contact reached pustular stage rather than as of the date vaccination was performed. Other observers estimate the incubation period as seven to ten days. In this connection, it is to be noted that lesions arising after the first crop tend to mature more quickly than do the original lesions.

Contributing Factors.—Eleven of our patients gave a history of infantile atopic eczema. One patient receiving antisyphilitic therapy had an arsenical dermatitis. Two others had concurrent dermatoses, eczemoid in character but not specifically classified, while in the last patient the vaccinia was superimposed on varicella. Nimpfer[8] reported four cases of generalized vaccinia lesions in patients suffering from burns, thus adding another group highly susceptible to vaccinia virus. Parenthetically, it is interesting here to note that several hundred patients with varicella were vaccinated against smallpox, in the usual manner, at Willard Parker Hospital, and so far as is known only one developed generalized vaccinia lesions.

Diagnosis.—The clinical diagnosis of generalized vaccinia lesions was usually made without difficulty. All case histories included some concurrent skin

disease, a recent smallpox vaccination either in the patient or his close contacts, and a negative history for exposure to variola. The presence of multiple, pustular umbilicated lesions, asymmetrically distributed, associated with pruritis, toxicity, and fever, completed prerequisites for clinical diagnosis. Subsequent immune reaction to smallpox vaccination in children never before vaccinated may also be considered significant.

Laboratory tests, while most useful in the hands of experienced technicians, are not usually available, and the final diagnosis in most cases must rest upon the clinical findings. The diagnostic methods of choice are the Paul test, the complement fixation test, and the neutralization test. A fourth method as developed by Hirst[9] consists in identification by growth characteristics on the chorio-allantoic membrane of eggs. The virus of smallpox, obtained from persons with active cases of the disease who were in the hospital at the time, produced a growth pattern which was easily differentiated from that of the vaccinia virus.

A modification of the Paul test in this series was helpful, although in five cases there were negative or unsatisfactory results. The modified Paul test was performed by inoculating a rabbit's cornea with the crusted material from a vaccinia lesion. Upon the development of a definite gross keratitis, sections of the tissue were examined microscopically for Guarnieri bodies. Complete bone marrow studies on five patients in this series failed to reveal any characteristic abnormalities.

Differential Diagnosis.—In the differential diagnosis, one must consider impetigo, variola, erythema multiforme bullosa, postvaccinal urticarial reactions, and multiple vaccination (complications of vaccination which we observed). Other diseases that may be confused with generalized vaccinia include herpes zoster and pustular syphilis.

In impetigo, the lesions are seldom umbilicated and fever is not a usual accompaniment. Variola may occur within the first five to six days after a vaccination, and diagnosis in most cases must rest upon history and clinical manifestations. There was seldom a history of prodromata in the patients with generalized vaccinia whom we observed, while the eruption of variola is characteristically preceded by headache, backache, and malaise. The early lesions of a generalized vaccinial infection are full-blown umbilicated vesicles, while those of variola are firm, salmon-pink nodules, which only later develop frank vesiculation. We observed no cases of generalized vaccinia lesions on the mucous membranes, a typical site for variola lesions. Continuation of fever after the appearance of the eruption occurs regularly in generalized vaccinia though not in variola. Erythema multiforme bullosa and urticaria-like lesions may occur following vaccination, but these conditions are not easily confused with generalized vaccinia. Multiple vaccination is characterized by autoinoculation of only one or two lesions, usually on the face or hands. Herpes zoster typically follows a nerve trunk and is very painful, thus enabling differentiation from vaccinial lesions, which have no predilection for nerve trunks and appear to cause only a pruritis. Pustular syphilis can usually be definitely diagnosed by history and serologic tests.

Course of the Disease.—The onset, as mentioned previously, was not accompanied by the rather severe prodromata characteristic of variola. The first manifestation, in most cases, was the appearance of multiple lesions, either about the vaccination site or elsewhere, followed by fever, prostration, and regional lymphadenopathy. The course was, in most cases, remarkably rapid, especially in those who contracted the virus from the vaccination of close contacts. The two fatalities observed in the series occurred in infants who had never been vaccinated.

In most cases there was a rapid spread and progression of the lesions on the second day of illness. The temperature frequently reached 105° F., and prostration was severe at this time. From the second to the seventh days of the illness, successive crops of lesions erupted over different areas of the body. There was a definite affinity for eczematoid tissue, but skin which had previously appeared healthy was involved also to a lesser extent. In only four instances were there lesions on the palms and soles, and in none of the cases were lesions present on the mucous membranes. The temperature of the less severely affected patients usually had subsided to normal by the fifth or sixth day of illness. In some of the more critically ill patients the temperature persisted as high as 104° F. until the eighth or tenth day. Toxicity ran closely parallel to the fever in its severity. With the fall in temperature, the appetite increased and the patient appeared to be in far better spirits.

The lesions, in the early stages, were umbilicated pustules. These frequently coalesced to form a mat of pustules, which soon broke down to leave a denuded, weeping area. This was frequently noted over the more severely affected eczematoid areas. The individual lesion was, on the average, from 6 to 10 mm. in diameter. In the isolated lesion a mild erythematous areola could be seen, but this was not comparable to that seen in the usual solitary reaction following intentional vaccination.

The umbilicated pustular form persisted for six to twelve days, when the lesion became rather heavily crusted and slightly larger than the original. This stage lasted for a variable period, desquamating and leaving an atrophic pale pink macule of corresponding size. Eczematoid tissue, where there was a confluence of the lesions, tended to be scarred, while the individual lesion left a barely perceptible blemish. Follow-up of vaccinia cases occurring in Negro patients showed considerable loss of pigment in the more severely involved areas.

Dissemination of Virus.—Ellis[10] felt that the cutaneous distribution in eczema vaccinatum was due to hematogenous spread. Tedder[11] believes that true generalized vaccinia is "a disturbance (following vaccination) of the balance between virus and the virucidal substances which it calls forth in a person having an intact healthy skin, so that the virus which is disseminated hematogenously becomes active in the skin, producing a generalized vesicopustular eruption, lesions on the mucosa and general symptoms." He adds: "Eczema vaccinatum in most instances represents inoculation even when the eruption is widely spread over the body."

It is now generally accepted that in an uncomplicated smallpox vaccination the virus is disseminated throughout the body by the circulation (Gins,[12]

Paschen,[13] Jubb,[14] Leake,[15] and others). Thus one must assume that in generalized vaccinia, whether or not contributed to by an underlying eczema, there is a hematogenous dissemination of the virus throughout the body. If, in atopic eczema, the multiple lesions arise by hematogenous spread, then it must be presupposed that the portions of the skin affected by eczema are areas of lowered resistance to blood stream implantation of the virus. Against this hypothesis is the fact that when multiple vaccinial lesions occur in those persons themselves vaccinated, they tend to appear first, but not invariably, as a satellite crop around the vaccination and later appear in eczemoid areas. Hematogenous spread of the vaccinia virus results in the presence of the virus in the nose and throat secretions of individuals vaccinated four to five days previously. This probably accounts for the cases of generalized vaccinia in those who are unvaccinated and have not had known direct contact with the vaccination area of another individual.

Clark,[6] in commenting upon three cases in the Edinburgh series, which three he designated as "heterogenous vaccinia," states that "the cases had certain features in common—(a) the children were all under 5 years of age, (b) none of them had ever been vaccinated, (c) all were having ointment inuncted for concurrent skin disorders, and (d) other members of the household were having vaccinial reactions dressed." Subsequently, in these three patients, vaccinial lesions appeared in the areas inuncted.

Treatment.—Our experience with generalized vaccinia lesions leads us to suggest the following treatment:

1. The suppression and prevention of secondary infection by the use of parenteral penicillin and saline compresses or penicillin ointment locally as indicated.

2. The prevention of further allergic reactions by removing from the diet the usual allergenic foods, including milk, orange juice, chocolate, wheat, and egg.

3. The prevention of further autoinoculation through restraint of infants from scratching. This was best accomplished by the following combination of methods: (a) The patient was placed in such a position as to minimize friction between the bed and the most extensively involved area. (b) Elbow splints were applied. (c) Fingernails and toenails were clipped short, and the hands were covered with white cotton stockings. (d) The involved areas were further protected by the application of protective dressings with penicillin ointment. (e) An eczema jacket may be used, but it is believed that no effort should be made toward body immobilization because of the danger of hypostatic pneumonia or respiratory obstruction from aspirated vomitus.

4. The maintenance of adequate hydration and of the proper balance of the body electrolytes was of course important, particularly in the infants with extensive involvement.

NOMENCLATURE AND CLASSIFICATION

Cases of generalized vaccinial lesions have received a number of different designations, and as a result the multiplicity of synonyms is confusing. Ron-

chese[16] lists the following: Kaposi's varicelliform eruption, pustulosis vacciniformis acuta (Freund), eczema vaccinatum, pustulosis acuta varioliformis (Juliusberg), postvaccinial eruption, generalized vaccinia (Venturi), eczema varicellatum (or variolatum), and eczema herpetiforme. Ronchese, himself, used the term dermatitis vaccinia. Because many of these terms were employed at a time when there was little knowledge of bacteriology and no knowledge of viruses, description rather than etiology was the primary consideration. For this reason, it cannot be said that the individual lesions in each case, described by these various titles, contained the virus of vaccinia or that they were produced by only one etiological agent.

In recent years, the confusing nomenclature has been partially clarified by the elimination of several synonymous terms, but enough are still in common usage to create misunderstanding. While others are occasionally employed, the three designations generally accepted for the presence of multiple lesions of vaccinia are: Kaposi's varicelliform eruption, eczema vaccinatum, and generalized vaccinia.

The first of these, Kaposi's varicelliform eruption, is a descriptive term which has been applied to any eruption resembling varicella (or vaccinia) when it occurs on an eczematous child. The etiology has been ascribed to a host of organisms, including the streptococcus, the virus of herpes simplex, and the virus of vaccinia. Kaposi himself appears to have felt that the causative agent might be a fungus.

The inclusion of manifestations of several distinct and separate organisms under one diagnosis was probably justified in 1887 when Kaposi described his "alarming complication of eczema." But although the lesions of the herpes virus, the streptococcus, and vaccinia on or in the skin of an eczematous infant may exhibit superficial similarity, it must be remembered that each of these infecting agents produces different systemic and local reactions, so that under the Kaposi designation any one of at least three pathologic conditions might be involved. The significance and preciseness of such a term as "Kaposi's varicelliform eruption" is open to question. There is some logical objection, too, to utilization of the word "varicelliform" in a condition that is not varicella or any modification of it, but is, in fact, vaccinia. Such a designation is not only confusing from the standpoint of etiological understanding, but is misleading even as a descriptive term.

In the circumstances, and for the sake of clarity, it would seem appropriate to consider etiology rather than gross appearance as a basis for nomenclature in this instance, and when the virus of vaccinia is present, to use the term "generalized vaccinia."

A second cause of confusion in terminology seems to have arisen from the assumption that in those cases where multiple lesions of vaccinia appear upon a healthy skin, the spread was hematogenous from the initial lesion of vaccinia; and that when similar multiple vaccinial lesions occur in a person with eczema (whether the initial lesion of vaccinia was caused purposely or accidentally) the spread was by a series of individual surface implantations. Apparently, some observers have tended to base terminology upon this assumed pathogenesis and

TABLE I. SUMMARY DESCRIPTION OF FIFTEEN PATIENTS WITH GENERALIZED VACCINIA OBSERVED AT WILLARD PARKER HOSPITAL FOR CONTAGIOUS DISEASES IN THE PERIOD APRIL-JUNE, 1947

CASE NO.	AGE	SEX	RACE	VACCINATION OR EXPOSURE TO VACCINATION	INCUBATION PERIOD* (DAYS)	DISTRIBUTION GENERALIZED VACCINIA LESIONS	UNDERLYING SKIN CONDITION	WHITE BLOOD CELLS (THOUSANDS)	LABORATORY FINDINGS			OUTCOME
									SYPHILIS SEROLOGY	PAUL TEST	RECOVERY OF VACCINE VIRUS†	
1	3 mo.	M	N	Mother vaccinated 4/14	19	Face, scalp, arms, trunk, legs, 1 on palm	Atopic eczema	13.1	Neg.	Pos.	Pos.	Recov.
2	8 mo.	M	W	Parents vaccinated 5/2	14	Over all of body, not on soles, 3 on left palm	Atopic eczema	12.8	Neg.	Neg.	Pos.	Died
3	9 mo.	M	N	Mother vaccinated 4/17	9	Head, face, shoulders, neck, dorsum, feet	Atopic eczema	12.0	Neg.	‡	Pos.	Recov.
4	28 mo.	M	W	Own vaccination 4/17	6	Back, neck, shoulders, extremities	Atopic eczema	11.0	Pos.	‡	Pos.	Recov.
5	6 mo.	M	N	Mother vaccinated 4/20	13	Head, scalp, arms, legs	Atopic eczema	11.5	Neg.	Not done	Pos.	Recov.
6	11 mo.	M	N	Brother vaccinated 4/19	20	Face, hand, thigh	Atopic eczema	10.0	Neg.	Pos.	Pos.	Recov.
7	13 wk.	F	N	Mother vaccinated 4/25	8	Face, scalp	Atopic eczema	15.8	Neg.	Pos.	Pos.	Recov.
8	4 mo.	F	W	Family vaccinated 4/17	19	Face, arms, legs, palm	Atopic eczema		Neg.	Pos.	Pos.	Died
9	58 yr.	M	N	Vaccinated 4/18	2	Face, arms, legs, neck, trunk	Chronic eczema; cause?		Neg.	Pos.	Pos.	Recov.
10	2 yr.	M	N	Vaccinated 4/14	2(?)	Right arm, right shoulder, and right upper thorax	Atopic eczema	12.7	Neg.	Not done	Pos.	Recov.
11	42 yr.	M	N	Vaccinated 4/13	7	Right arm and forearm	Arsenical dermatitis	11.6	Pos.	‡	Pos.	Recov.
12	64 yr.	F	N	Vaccinated 4/9	6	Arms, legs, few on trunk	Eczema; cause?	10.3	Neg.	Pos.	Pos.	Recov.
13	2 yr.	F	W	2 brothers, parents vaccinated 5/10	16	Face, popliteal, right groin, elbow	Atopic eczema	24.5	Neg.	Pos.	Pos.	Recov.
14	3½ yr.	M	W	Own vaccination 4/18	6	Face, arms, popliteal	Chronic atopic eczema	14.2	Neg.	Pos.	Pos.	Recov.
15	6 yr.	M	N	Vaccinated 4/19	6	Chest, abdomen	Varicella	Not determined		‡	Pos.	Recov.

*Calculated from informants' statements. †Chorio-allantoic membrane, embryonated egg. ‡Unsatisfactory.

would thus limit use of the term "generalized vaccinia" to the appearance of multiple lesions of vaccinia on a skin healthy and intact other than for the initial vaccinial lesion, and to designate as eczema vaccinatum only those cases in which multiple lesions appear on an individual with eczema. But even if the mode of dissemination constituted a sound base for nosology, it has not been demonstrated that multiple vaccinial lesions in a healthy skin arise only through hematogenous spread or that those on an eczemoid base are never similarly spread. Actually, of course, the virus of vaccinia has repeatedly been shown to be present in the blood stream, and once the virus is introduced, either purposely or accidentally in a child with eczema or with a healthy skin, the spread could be either hematogenous or by external autoinoculation. Regardless of the manner of spread of the virus, multiple lesions of vaccinia in persons with eczema and in those without differ only from the standpoint of susceptibility of the skin: In both instances, generalized vaccinia is present. Even though the underlying eczema may predispose to generalization of vaccinia, eczema and vaccination are separate conditions, and it would not seem justifiable to employ a designation such as eczema vaccinatum, which would suggest that together they constitute a third entity.

In view of these various considerations, generalized vaccinia is perhaps the generic term of choice, whether or not the condition is complicated by eczema.

CONCLUSIONS

1. Fifteen cases of generalized vaccinia are reported with recommendation for treatment.

2. Patients with eczema and burns should not be vaccinated, nor should they remain in the same household with those recently vaccinated.

3. Postvaccination complications in atopic eczema strongly suggest the advisability of vaccination during the first few months of life before the onset of most allergic skin conditions and before the acquisition by the infant of "scratchability."

4. It is important that every individual being vaccinated against smallpox be questioned concerning active eczematous conditions in himself or in members of his household. In the presence of the first condition the vaccination should be postponed until subsidence of the eczema. In the presence of eczema in a member of the household, the vaccinated individual should live apart from the eczematous individual until completion of the vaccination reaction.

5. "Kaposi's varicelliform eruption" should be regarded only as a descriptive term and not as a clinical entity. The term should not be employed when etiology has been established. Generalized vaccinia is the term of choice.

We are indebted to Dr. George K. Hirst, Chief of the Division of Infectious Diseases, Public Health Research Institute of New York, for his work on vaccinia cultures, and to Dr. Vera Dolgopol, pathologist of the Willard Parker Hospital staff, for reports on the Paul test.

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A CASE HISTORY OF BREAST FEEDING SUCCESSFULLY ESTABLISHED DURING THE THIRD POST-PARTUM WEEK ON A SELF-REGULATING FEEDING PROGRAM

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FEW questions are of more practical or theoretical importance for the physical and psychological welfare of the mother and her newborn baby than the question of breast feeding. Yet, despite the importance of the question, scientific information concerning the prognosis for successful breast feeding is meager, although many theories concerning the reasons for the low incidence of successful breast feeding in our society have been advanced. Because of our meager information regarding the prognosis for breast feeding, the following case of the successful establishment of breast feeding after the fifteenth post-partum day is worthy of study. Before turning to a discussion of the case, a brief review of some of the available research is indicated.

REVIEW OF RESEARCH

Mead[1] has reported that among the Mundugumor of New Guinea some adoptive mothers who have never borne infants or who have not suckled a child for many years can develop a secretion of breast milk under the stimulating effect of a child's sucking combined with drinking large quantities of cocoanut milk. Stewart and Pratt[2] in a study of 900 successive cases of breast feeding found that no case of deficient lactation increased to full breast nursing by the tenth postpartum day. They have, however, presented data which suggest that the suckling stimulus may account for the higher incidence of full breast nursing among primiparas who place their babies early on both breasts.[3] Selye[4] has demonstrated the important role of the suckling stimulus in the lactation of normal animals.

FEEDING HISTORY OF CHILD M

Early Feeding History.—Child M, a normal infant weighing 8 pounds, 1 ounce, was delivered by cesarean section. Although the mother was eager to breast feed her infant, her condition following delivery made it impossible to initiate breast feedings until the fifth post-partum day. From the fifth through the fifteenth day of the infant's life he was offered breast feedings five and later six times daily in accordance with usual hospital practice. In addition he received supplementary feedings. During this hospital period, the infant never received more than one ounce of breast milk at any feeding. His nursings at the breast lacked vigor and he often fell asleep early in the nursing period.

*Mother of the infant.

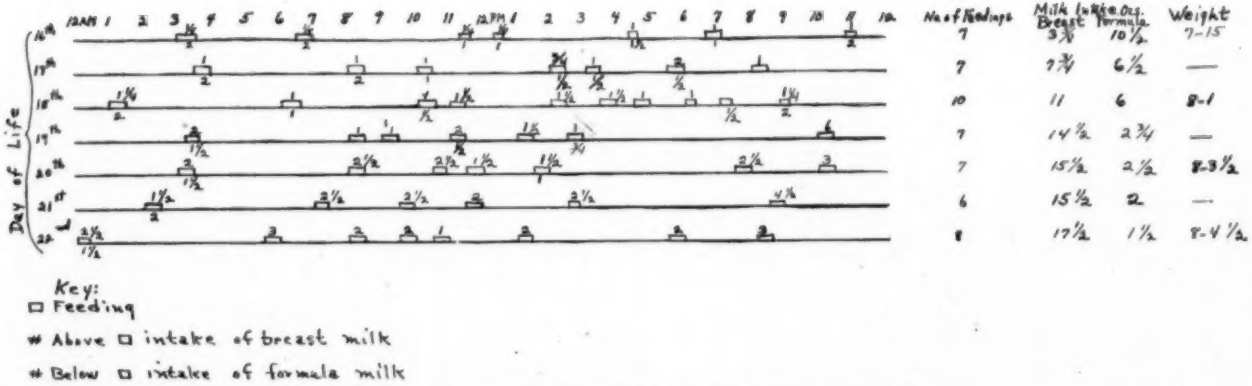

Chart 1.—Behavior day chart, first week of self-regulating feedings.

Initiation of Self-Regulating Feedings.—Scheduled feedings were abandoned on the fifteenth day when the mother and baby returned from the hospital. Detailed feeding records were commenced on the sixteenth day of the infant's life, the first full day of self-regulating feedings. During this early period at home supplementary bottle feedings were given immediately following the breast feeding and an effort was made to keep the feedings as small as possible with the aim of having the infant sufficiently hungry to nurse vigorously at the breast. The program was undertaken under the guidance of a pediatrician and with the aid of a pediatric nurse. As the infant became launched upon this program the mother soon observed marked differences in the nursing behavior. The infant nursed at the breast more vigorously and for longer periods, some of the nursings lasting for one-half hour or longer.

Feeding History During the First Week of Self-Regulating Feedings.—Chart 1 plots the feeding history during this first week of self-regulating feedings, from the sixteenth through the twenty-second days of life, and shows the approximate amounts of intake of breast and bottle milk. The total intake of 3⅝ oz. of breast milk on the sixteenth day of life with an intake of only ⅛ oz. at three of the feedings confirms the hospital feeding history of an almost negligible amount of breast milk intake. As Chart 1 shows, the total daily intake of breast milk increased during this week to 17½ oz. in eight feedings during the twenty-second day of life. This increase in breast milk intake was accompanied by a decrease in the amount of formula milk taken. On the sixteenth day the infant took a total of 10½ oz. of formula milk, but on the twenty-second day he took only 1½ oz. During this week, as the chart shows, the infant gained 5½ oz. He took a total of fifty-two feedings, a number considerably in excess of the six daily feedings that had been planned for him during the hospital period.

Feeding History from the Twenty-third Through the Fifty-eighth Day of Life.—Chart 2 shows the number of daily feedings from the sixteenth through the fifty-eighth day of life, the amount of intake of breast or formula milk and the amount of weight gain. Following the twenty-second day, the mother maintained a supply of breast milk adequate, or nearly adequate, to meet the infant's apparent needs. One or very occasionally two complementary bottle feedings were given each day commencing with the twenty-sixth day of life. These complementary feedings were often given in lieu of the early morning breast feeding in order that the mother might have a longer uninterrupted sleep. Occasional supplementary bottle feedings were given. During the week from the forty-fourth to the fifty-first day of life the mother secreted on the average about 22½ oz. of breast milk each day. Thus breast feeding had been successfully established.

Spontaneous Scheduling.—Child M, like other self-regulating infants who have been studied spontaneously, reduced the number of his daily feedings but it is notable that it was not until the eighth week of life that he took as few as thirty-six feedings during the week. Also like other self-regulating infants whose feeding histories have been recorded, he showed a marked tendency to

take his longest sleep after his late afternoon feeding or occasionally even after a midafternoon feeding. On his forty-third day of life he slept from 6:30 P.M. until 1:00 A.M. On four days during the following two-week period he slept for intervals of approximately ten hours, commencing these sleeping periods about 6 to 7 P.M. On his fifty-eighth day of life he slept from 2:00 P.M. to 1:00 A.M.

Chart. 2.—Daily intake of breast and formula milk, weight gain, and number of daily feedings, sixteenth through fifty-seventh day of life.

COMPARISON WITH OTHER SELF-REGULATION INFANTS

Child M's feeding picture is so similar in certain aspects to the feeding picture in the case of the two infants studied by Simsarian and McLendon[5] that comparisons seem appropriate. All three infants took more than fifty feedings during a week in the early weeks of self-regulating feedings and as many as ten and eleven daily feedings on some days during the early period of adjustment. All three protracted their nursings for thirty minutes or longer at some feedings, particularly during the early period. This tendency to protract some nursings was also observed in twin infants studied by Trainham et al.[7] However, these latter infants took few feedings, never more than thirty-five feedings during a single week. Unquestionably as more and more children on self-regulating schedules are studied we will gain new insights into some of the ways in which different parental handling as well as other factors may affect the feeding picture.

SUMMARY AND EVALUATION

The mother's intense desire to nurse her infant is attested to by her eagerness to continue nursing even in the face of what appeared to be an unfavorable prognosis at the time when mother and baby left the hospital. The mother derived such pleasure from nursing the infant that she felt more than amply rewarded for the unusual efforts which she had made.

A mother who produced only a negligible amount of breast milk for her infant during the fifteen days of hospitalization was able to produce a supply of breast milk adequate, or nearly adequate, to meet her infant's needs during the first week at home when the infant was placed on a self-regulating schedule. The infant took a total of fifty-two feedings during this week increasing the daily amount of breast milk taken from 3⅝ oz. on the sixteenth day to 17½ oz. on the twenty-second day. Similarities to other case histories of self-regulating feeding have been noted.

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PERTUSSIS IN INFANCY

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WHOOPING cough is no doubt the most devastating acute infectious disease of infancy, exacting its heaviest toll particularly during the first year of life. When the current incidence and mortality are viewed historically, it may appear that whooping cough has become a mild disease, but the fact still remains that it poses one of the severest hazards to the life of the infant. Sauer[1] and Lapin[2] have repeatedly written that pertussis is an extremely serious disease during infancy. Davis and Carroll[3] have recently studied the mortality from whooping cough in Texas. In 1943 there were one-third more deaths attributable to whooping cough than to diphtheria, measles, and scarlet fever combined for all age groups. In children under the age of one year, whooping cough caused nearly seven times as many deaths as the other three diseases combined.

CLINICAL MATERIAL

The present study is an analysis of 137 patients under the age of 2 years admitted to The Infants' and Children's Hospitals in Boston between 1931 and 1945 with a diagnosis of whooping cough. Of this group, forty-five were treated with pertussis hyperimmune serum,* or a globulin concentrate derived from hyperimmune human serum† after admission to the hospital. Since pertussis hyperimmune serum was not used at The Infants' and Children's Hospitals prior to January, 1941, patients admitted before that date are included as a background for comparison with the serum-treated group. A subsequent follow-up study is planned in order to observe the long-term effects of this disease when it occurs in the first two years of life. No evaluation of serum therapy is possible unless the two groups are comparable as regards the severity of the disease before institution of specific therapy.

In order to compare the severity of disease in the serum-treated group with that in the group not receiving serum we have listed in Tables I through VII certain statistical findings applicable to both groups of patients. In these tables the group receiving serum after admission is called Group A, and the one which did not receive serum is Group B.

1. *Age and Sex.*—The age and sex distributions of the patients studied, divided into two groups according to whether serum was used in treatment, are presented in Table I.

According to Table I the average age of the patients in Group A was two and one-half months younger than that of the patients in Group B. There was

From The Infants' and Children's Hospitals, Boston.

*Distributed by the Serum Exchange, Philadelphia Children's Hospital.

†Concentrated human hyperimmune pertussis globulin (Hypertussis) was prepared and kindly supplied by the Cutter Laboratories of Berkeley, Calif.

TABLE I. AGE AND SEX DISTRIBUTION

AGE IN MONTHS	GROUP A		GROUP B	
	BOYS	GIRLS	BOYS	GIRLS
22-24	0	0	3	1
19-21	0	1	2	2
16-18	0	0	3	3
13-15	1	1	2	5
10-12	1	3	3	5
7- 9	6	3	9	6
4- 6	7	2	3	17
1- 3	10	10	13	15
Totals	25	20	38	54
Total Number	45		92	
Average Age	5.9 months		8.5 months	

no attempt to select cases. All critically ill patients admitted after hyperimmune serum became available received this therapeutic agent.

2. *Duration of Disease Prior to Hospital Admission.*—In estimating the length of time during which the disease was present prior to hospital entry, the onset of cough was taken as the beginning of the disease, since this sign is more reliable than such signs as malaise, irritability, restlessness, or coryza. In Table II there is presented a distribution of the intervals during which coughing was present before hospital admission.

TABLE II. DURATION OF DISEASE BEFORE HOSPITAL ADMISSION

DAYS	GROUP A	GROUP B
60-69	0	1
50-59	0	0
40-49	0	2
30-39	1	5
20-29	8	23
10-19	20	28
0- 9	16	33
Total	45	92
Average	13.7 days	16.2 days

As a rule, patients were not referred to the hospital unless more alarming signs and symptoms than coughing were present. It was usually these additional signs and symptoms which were responsible for the eventual admission of the patient.

3. *Signs and Symptoms.*—In Table III there are listed the signs and symptoms present in the patients at the time of hospital admission.

The cough of pertussis differs from other coughs observed in infancy chiefly because of its paroxysmal nature, each coughing outburst initiating in trigger

TABLE III. FREQUENCY OF SIGNS AND SYMPTOMS ON ADMISSION

SIGNS AND SYMPTOMS	GROUP A		GROUP B	
	NUMBER	PER CENT	NUMBER	PER CENT
Paroxysmal cough	45	100	92	100
Vomiting	31	70	66	72
Cyanosis	30	67	51	55
Whoop	13	29	30	33
Convulsive episodes	10	22	16	17
Anorexia	3	7	17	18

fashion a series of coughing reflexes of progressive intensity. In the absence of paroxysmal coughing, observed in every patient studied, the clinical diagnosis of pertussis cannot be made safely.

Next in frequency was vomiting, observed in 70 per cent of the patients and occurring at the end of, or in the midst of, a coughing paroxysm and not usually present as a sign independent of the cough. Anorexia did not seem to accompany vomiting, and as can be seen from Table III, it occurred rather infrequently.

Cyanosis occurred with distressing frequency, particularly among the younger patients. The inspiratory crow, termed the "whoop," was present in only about one-third of the patients.

Convulsive episodes, which could not be attributed to other causes, occurred more frequently in the patients of Group A. Both clonic and tonic movements were observed, rolling back of the eyes, staring, and apparent loss of consciousness. In one patient, convulsive movements were present continuously from the moment of admission to her death several hours later.

4. *Laboratory Data.*—Laboratory procedures were usually limited to routine blood counts and bacterial cultures by means of cough plates and nasopharyngeal swabs. The degree of leucocytosis is listed in Table IV. Each blood count represented in Table IV was the highest count obtained during the patient's hospital treatment.

TABLE IV. DEGREE OF LEUCOCYTOSIS (HIGHEST WHITE BLOOD COUNT OBTAINED DURING HOSPITALIZATION)

WBC (THOUSANDS)	GROUP A	GROUP B
130 and above	1	1
110—129	0	1
90—109	0	2
70— 89	2	4
50— 69	4	8
30— 49	16	20
20 and below	22	52
Number	45	88
	(No WBC reported on four patients)	
Average WBC	37.3 thousands	34.3 thousands

The degree of lymphocytosis varied from 40 to 90 per cent, the majority of blood smears showing 60 to 80 per cent lymphocytes. A predominance of lymphocytes was present in approximately 75 per cent of the smears.

From our records it appears that the bacteriologic diagnosis of pertussis is a difficult procedure. Until recently the most common practice was to hold an open Bordet-Gengou (B.G.) plate before a coughing patient, a technique which has not proved satisfactory. In 1942, Brooks and his associates[4] described the advantages of their nasopharyngeal culture over the traditional cough plate culture in obtaining bacteriologic evidence of whooping cough infection. Silverthorne and his co-workers[5] have found that a direct smear of nasal mucus produced 80 per cent positives in showing gram-negative bacilli. Cough plate cul-

tures in their series gave 55 per cent positives. In Table V are listed the results of cultures of B.G. cough plates and of nasopharyngeal swabs.

TABLE V. CULTURES OF B.G. PLATES AND NASOPHARYNGEAL SWABS

	GROUP A		GROUP B	
	POSITIVE	NEGATIVE	POSITIVE	NEGATIVE
B.G. cough plate	1	6	4	25
Culture of nasopharyngeal swab	13	22	1	40

In the remainder of the patients either no attempt was made at bacteriologic diagnosis or contamination of cultures occurred. These figures probably serve only to show that the handling of pertussis cultures in a routine hospital laboratory is not satisfactory. The low incidence of positive cultures for the patients in Group B, most of whom were admitted prior to 1941, merely serves to show that in the absence of specific therapy less pains are apt to be taken to make an accurate laboratory diagnosis. When special care is taken by a trained technician in obtaining and culturing the organisms, as has been done recently, a much higher percentage of positive cultures is obtained.

5. *Complications.*—In Table VI are listed the complications encountered in the present series of cases and their relative frequency. These complications were present when the patients were admitted.

TABLE VI. FREQUENCY OF COMPLICATIONS IN PERTUSSIS AT TIME OF ADMISSION

COMPLICATION	GROUP A		GROUP B	
	NUMBER	PER CENT	NUMBER	PER CENT
Pneumonia	22	46	47	51
Bronchitis	6	13	13	14
Otitis media:	12	25	18	20
Nonsuppurative	(7)		(5)	
Suppurative	(5)		(13)	
Encephalopathy	7	15	12	13
Atelectasis	2	4	2	2
Emphysema	1	2	3	3
Nutritional disturbances	2	4	5	5
Umbilical hernia	1	2	4	4

The most frequent complication, and also the most serious, was pneumonia, present in approximately 50 per cent of the patients. According to the roentgenographic descriptions, the pneumonic process was usually interstitial or peribronchial in type. Until the advent of sulfonamides the mortality from this complication was appallingly high.[6] For the purpose of this study a diagnosis of pneumonia was not tabulated unless there was x-ray evidence of a pneumonic process. In the absence of this confirmatory evidence, but when the breath sounds were altered in character, when there was an acceleration of respiratory rate, and when respiratory distress was apparent, a diagnosis of bronchitis was made. It is felt that in these patients the differences between pneumonia and bronchitis were probably quantitative rather than qualitative.

The next most frequent complication was otitis media, both the nonsuppurative and suppurative types occurring. In Group A twelve cases occurred, whereas in the other group eighteen cases were observed.

There were nineteen cases of encephalopathy, seven in Group A and twelve in Group B. Convulsive seizures were observed in all nineteen patients. From the standpoint of prognosis, convulsive seizures were a bad sign since every patient who eventually died exhibited this sign early in his hospital course.

Atelectasis, emphysema, umbilical hernia, and nutritional disturbance each occurred in 5 per cent of the patients, or less, as shown in Table VI. A diagnosis of nutritional disturbance was made when there was persistent diarrhea with attending loss of weight and dehydration, although food intake was not necessarily diminished.

TABLE VII. DATA ON EXPOSURE

HISTORY OF EXPOSURE	NUMBER OF CASES
Intimate exposure to member of same family at home	69
Casual exposure in neighborhood or in same apartment	26
No known exposure	42

6. *Data on Exposure.*—In 69 patients accurate and satisfactory data on exposure were obtained. In these cases there was at least one sibling at home with signs and symptoms of the acute stage of pertussis which would account for the patient's exposure. In twenty-six additional patients the history of exposures was less definite, being in the nature of a casual contact with a coughing person living in the immediate neighborhood. In the remaining forty-two patients no history of exposure was obtained, although in all cases such a history was sought.

7. *Patients With a History of Pertussis Prophylaxis.*—In seven patients there was a history of prophylactic injections of pertussis antigen, but in five of these the procedure could not be considered adequate. One patient had completed a series of three injections of Sauer's vaccine three months before the onset of symptoms. This patient, a girl aged 18 months, was casually exposed to a child with whooping cough. She required only eight days of hospital care, chiefly because of the co-existence of a suppurative left otitis media and pneumonia. Her course was uneventful and she made a good recovery. In only one other patient was there a history of adequate prophylaxis. This was in a boy, aged 9 months, who had been admitted to the neurological ward with a diagnosis of chronic subdural hematoma one month after completing a series of three pertussis antigen injections. Exposure could not be satisfactorily determined. His course was rather uneventful.

Another of our patients was a 19-month-old girl who had received two injections of Sauer's vaccine, one at the age of 8 months, the second injection at 14 months. This was certainly not an acceptable method of immunizing against pertussis. Four other patients received subcutaneous pertussis antigen injections after the onset of symptoms, a procedure of no value whatsoever.

In our series no patient who received adequate prophylaxis and subsequently contracted whooping cough exhibited convulsive phenomena or showed evidence of a severe infection. We have been unable to find any recorded case in which a patient who had received adequate prophylaxis succumbed to pertussis or its complications.

In summary, the cases of pertussis observed in this hospital were quite severe, with a high incidence of complications, and the findings were typical of the classical descriptions of the disease in infancy. Cultural proof of the diagnosis was not obtained in most cases. Although serum has been used in treatment only since 1941 and for only the severer cases, a comparison of the serum-treated group with the group receiving no serum indicates that the two groups were very similar with respect to the various indices of severity, although the average age of the former group was somewhat lower than that of the latter group.

TREATMENT OF ACTIVE PERTUSSIS

1. *Convalescent Blood, Blood Derivatives, Sulfonamides, and Penicillin.*—Within recent years three new therapeutic agents have been employed in the treatment of active pertussis and its complications, exclusive of the supportive measures which have, no doubt, contributed to the speeding up of convalescence and to the lowering of mortality. These agents are pertussis hyperimmune serum and the sulfonamides and penicillin, usually employed in treating a complicating pneumonia or other secondary infections known to be sensitive to these two chemotherapeutic agents. From a review of the literature, it can be seen that many materials have been employed in treating whooping cough, but very few agents have withstood the test of time.

Cohen, Weichsel, and Lapin,[7] in a comparative study of Sauer's vaccine, typhoid vaccine, saline solution, convalescent serum, and hyperimmune serum used to treat active whooping cough, concluded that the first three agents had

TABLE VIII. HYPERIMMUNE SERUM IN THE TREATMENT OF WHOOPING COUGH

INVESTIGATOR	NUMBER OF CASES	NUMBER OF DEATHS	COMMENTS
McGuiness, Stokes, Mudd[12]	15	0	Small dosage employed. One-third showed much improvement
McGuiness, Bradford, Armstrong[13]	100	3	51 patients, 6 months of age and under. Results very good
Frank, Patton, Hamilton[6]	30	6	2½ to 3 c.c. of serum per pound of body weight. All patients had bronchopneumonia complicating pertussis; 20 per cent mortality
McGuiness, Stokes, Armstrong[14]	315	5	Mortality rate of 1.5 per cent. Excellent or good results in nearly 70 per cent
Scheinblum, Bullowa[18]	23	2	Sulfadiazine also given patients with pneumonia. Good results in 52 per cent, moderately good in 26 per cent
McGuiness, Armstrong, Felton[15]	442	6	55 of this group known to have pneumonia. Only ten patients received sulfonamides. Results on the whole excellent
Lapin[16]	25	0	Tenfold globulin concentrate of human serum employed. Marked or moderate improvement in 70 per cent
Kohn and his associates[17]	201	4	152 received human serum; 49 received rabbit serum; 2 per cent mortality

no merit but found that the two blood derivatives were of some value. The work of Silverthorne and Brown[8] with immune rabbit serum, and that of Bustamente and Zozoya[9] with immune goat serum would seem to indicate that both of these products are of value in prophylaxis and treatment but, to be sure, are not as practical or safe as homologous hyperimmune serum.

In 1935 Bradford[10] published a historical survey on the use of convalescent blood and blood derivatives in the treatment of active pertussis, concluding that convalescent serum or immune whole blood, if given before the onset of catarrhal symptoms, possessed protective qualities. In 1937 Meader[11] reported that 10 c.c. of pooled convalescent blood protected 67.8 per cent of 115 exposed children, whereas only 34 per cent of a comparable group of 183 exposed controls avoided developing pertussis. In Table VIII appears a summary of studies in which hyperimmune serum has been used to treat cases of active pertussis.

Felton[19] and Ewers[20] have recently reviewed the serum therapy of pertussis and concluded that it has definite value. Although the evidence in favor of serum is suggestive, the difficulty of establishing clear-cut criteria for evaluation, the general decline in mortality from pertussis and other infectious diseases, and the lack of alternate case controls in these studies prevent their being considered conclusive.

2. *Supportive Measures.*—Before presenting the results of the treatment of forty-five patients in our series with pertussis hyperimmune serum, we shall mention some of the more useful supportive measures which have been employed.

The restoration and maintenance of fluid and electrolyte balance are of paramount importance. Accordingly, intravenous saline and glucose were administered routinely to those patients whose state of hydration had been seriously altered. When it was found that serum proteins were diminished, casein hydrolysate and blood plasma were administered. Occasionally transfusions of whole blood have been given.

Sedation has nearly always been used. Phenobarbital, nembutal, paraldehyde, ether in olive oil per rectum, and cough syrups containing codeine have been employed frequently. In critically ill patients, oxygen therapy has been found of great value in diminishing cyanosis, while aspiration of the nasopharynx and oropharynx has lessened the number of choking episodes and apnea. Certain water-soluble vitamin preparations have been administered orally or parenterally. Peroral oily preparations should be avoided, owing to the hazard of lipoid pneumonia.

3. *Treatment in the Present Series.*—The patients are classified into four groups according to the therapy they received. In seventy-one patients therapy consisted of supportive measures exclusively; in twelve patients treatment consisted of sulfonamides plus supportive therapy; twenty-nine patients received sulfonamides, serum, and supportive therapy; the remaining sixteen patients were given serum and supportive treatment. After 1937 sulfonamides were administered to all patients in whom a diagnosis of pneumonia was made, or in whom there was an intercurrent infection known to respond to sulfonamides. In the patients who received pertussis hyperimmune serum the dosage paralleled

closely that recommended by McGuiness and his associates,[13] although in twenty-six patients the amount was below 60 c.c. (40 to 50 c.c.); nineteen patients received amounts between 70 and 100 c.c.

Clinically it has been found significant to follow the weight of infant patients in evaluating the progress of any disease as well as the effectiveness of its treatment. It is also a well-recognized fact that the weight of infants will vary markedly during the course of many diseases. In our patients this was true. In Table IX there are listed data on weight gain and weight loss during the period of hospitalization.

TABLE IX. WEIGHT GAIN AND LOSS DURING HOSPITALIZATION

WEIGHT RESPONSE	SERUM-TREATED	NO SERUM
Gained	25	38
Lost	10	25
No change	10	11

Upon being discharged from the hospital, sixty-three patients showed a gain over the admission weight, and thirty-five showed a weight loss. From Table IX it can be seen that there was no significant difference in terms of weight gain or loss in the two groups.

The patients who died were all in critical condition at the time of admission to the hospital. One patient, aged 4 months, showed signs of a severe encephalopathy upon admission, with increased pressure and 89 mg. per cent of total protein on lumbar puncture. She had had severe episodes of coughing at home for ten days prior to admission; her course was steadily downhill, and she died on the fourth hospital day. Post-mortem smears of the trachea for bacteria showed many *Hemophilus pertussis* organisms. Another patient was admitted at the age of 5 months. She had been coughing severely at home for approximately two weeks, having many episodes of cyanosis, and had been unable to retain food for ten days. Upon admission she was moribund, failed to respond to resuscitative measures, and died a few hours later.

In 1938 a 2-month-old girl was admitted with a three-week history of cough, cyanosis, and convulsive twitching. Her right upper lobe showed pneumonic consolidation. She failed to respond to all treatment and died six hours after admission. Another infant, aged 3 months, was admitted with a three-week history of paroxysmal cough, cyanosis, vomiting, and marked weight loss. The parents stated that the child had lost 5 pounds during this period of time. Upon admission this baby showed x-ray evidence of pneumonia and the clinical signs of meningism and marasmus. She lived for three days, receiving parenteral feedings and being maintained in an oxygen tent at all times. At autopsy, Type 29 pneumococci were recovered from her upper bronchi.

The most recent death from whooping cough occurred in a baby girl admitted in November, 1943, at the age of 14 months. She had been coughing rather violently for three weeks. Two older siblings at home had been coughing just as severely as the patient. However when the patient began to exhibit severe cyanosis and generalized convulsive movements, she was brought to the

hospital where the following diagnoses were made: pertussis, bilateral pneumonia, bilateral nonsuppurative otitis media, and encephalitis. Her temperature upon admission was 105° F. rectally, and it was noted in the clinical records that she was almost constantly in a convulsive state. She seemed to improve following a lumbar puncture, but then her temperature began to rise, finally reaching 108° F., whereupon she went into a continuous convulsive state and died seven hours after admission.

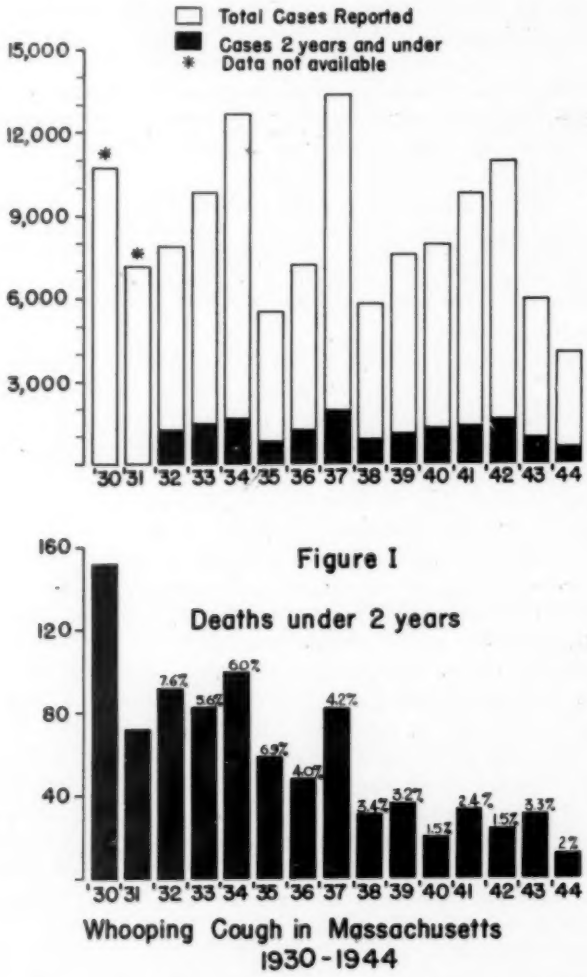


Figure I

Deaths under 2 years

Five of the nine deaths reported occurred during the first hospital day, two patients died during their second hospital day, one during the third, and one during the fourth. In this series of cases, if a patient were alive for three or four days following hospitalization, recovery was the rule.

The effectiveness of serum therapy cannot, at least in this series, be judged by the effect on case fatality rate alone, because it is our impression that in recent years pertussis has not been as serious a disease as previously. As can be seen from Fig. 1, which has been adapted from the Vital Statistics for the Commonwealth of Massachusetts, the number of deaths attributable to whooping cough has diminished markedly since 1930. Unfortunately, data for 1930 and 1931 on the number of cases in children under 2 years of age were not available. The percentages over the solid bars in the lower half of Fig. 1 refer to fatality rates based on the number of cases reported for children 2 years of age and under.* The fatality rate fell sharply to its average present level between 1935 and 1940.

The decline in mortality observed during the past fifteen years is probably due to a number of factors. In addition to the possibility that the disease is not as severe as it was previously, the introduction of sulfonamides with their effect in lowering the mortality attributable to complicating pneumonia, and the increasing popularity of pertussis immunization are to be considered. Supportive therapy has improved considerably, especially in the restoration and maintenance of fluid and electrolyte balance in vomiting patients.

TABLE X. FATALITY IN PRESENT SERIES

	SERUM-TREATED	NO SERUM			TOTAL FOR ALL CASES
	1941-1945	1932-1941	1941-1945	TOTAL	
No. of cases	45	67	25	92	137
No. of deaths	1	7	1	8	9
Per cent	2.2	10.4	4.0	8.7	6.6

In the present series of cases nine deaths occurred. One death occurred among the serum-treated group and eight in the other group. It is interesting to note that seven of the deaths in the group not treated with hyperimmune serum occurred prior to 1941. A total of twenty-five patients was treated after 1941 with agents other than pertussis hyperimmune serum, and in this group the fatality rate was 4 per cent. During the years under review the observed fatality rate of 6.6 per cent may appear unduly high, but it must be kept in mind that this rate applies only to hospital patients, and ordinarily infants with pertussis are not brought to the hospital unless they are critically ill.

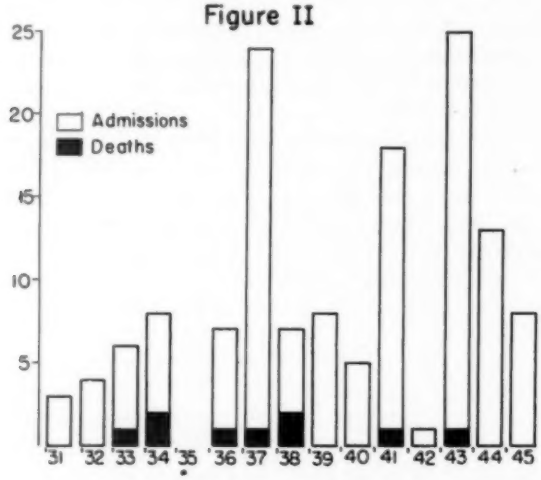
No attempt has been made in this study to correlate the type of therapy with actual duration of the disease. The length of the period of hospitalization was apparently influenced by the severity of the disease upon admission rather than by the type of therapy employed.

There has been a marked annual variation in the number of cases coming to The Infants' and Children's Hospitals for admission and in the number of deaths occurring during the years under review. (See Fig. 2.) In this series no deaths occurred after 1943, and only two deaths occurred between 1939 and 1945—that is, two deaths out of seventy-eight patients admitted during this interval.

*These percentages are actually of doubtful significance, because cases of whooping cough are generally very inadequately reported.

4. *Streptomycin.*—The effect of streptomycin in experimental pertussis in animals has been studied by Bradford and Day[21] and by Hegarty and his associates.[22] According to their preliminary reports, streptomycin should prove to be an extremely valuable drug in the treatment of clinical pertussis and is now being compared with serum therapy in this hospital.

Figure II



Whooping cough Admissions and Deaths
Under Two Years- 1931-1945

NEUROLOGICAL AND PSYCHOLOGICAL CONSIDERATIONS

Ellison[23] has summarized existing theories of the pathologic physiology of convulsive phenomena occurring during whooping cough. Mojumdar[24] has found that 41 per cent of encephalopathic complications occurring in the course of pertussis were observed in patients under the age of 2 years, the period when most fatal cases occur. According to this author, next to pneumonia, convulsive phenomena are the most common fatal complications.

Lurie and Levy[25] have studied personality changes following pertussis in a group of 500 problem children investigated at the Children's Guidance Home in Cincinnati. Among this group there were fifty-eight children who had been ill with whooping cough at the age of 2 years or younger. In 8.6 per cent of the group (of fifty-eight children) the authors felt there was a definite relationship between the attack of whooping cough and the behavior disorders which were responsible for referral of these patients to the Guidance Home. It is felt that the results of Lurie and Levy are inconclusive. In any unselected group of 500 children one would expect to find a history of pertussis in at least fifty-eight. Also, the entire group was made up of children with behavior disorders, so that it is inescapable that a history of pertussis could accompany the occurrence of behavior disturbances in at least part of the group. It would be more appropri-

ate to start with a group of children who are known to have had severe pertussis in infancy and then to study them at intervals of five and ten years in order to evaluate their subsequent progress and to compare their development with the parallel development of their siblings.

A follow-up study dealing with the patients here reviewed is now in progress. It is planned to do physical examinations, psychologic examinations, and laboratory studies on all the patients whom we are able to re-examine. We are especially interested in discovering the existence of any chronic respiratory disease in the patients known to have had severe pertussis. We plan also to evaluate their social and educational development in terms of the absence or presence of behavior disorders, and school progress. It will be especially worth while to compare them in these respects with children who may have escaped the disease at comparable age periods.

DISCUSSION

In the absence of any predetermined experimental plan, it is impossible to evaluate serum therapy in the present study. There has been no significant difference between the serum-treated and the non-serum-treated patients in terms of fatality rate since 1941, when serum was first introduced, but during that time serum has been given to the more severely ill patients, so that no adequate controls are available. In the whole period, 1931 to 1945, the fatality rate in the larger no-serum group was significantly higher than in the severely ill group of patients receiving serum after 1941, but factors such as the general decline in pertussis mortality and improvements in supportive therapy may explain this finding. Other criteria, such as gain or loss in weight, or duration of hospitalization, have failed to show significant differences in favor of serum therapy. We have not found it possible to keep sufficiently accurate records of the number of coughing paroxysms or cyanotic episodes occurring each day to use these direct manifestations as criteria of the progress of the disease. Perhaps a follow-up study may reveal differences, in either the incidence of chronic respiratory disease or in psychologic development, which may serve as criteria for the severity of the acute disease. From the standpoint of the patient as a whole these may be the most important aspects of pertussis, and therapy should be evaluated in terms of its ability not only to lower mortality but also to diminish prolonged impairment of health or reduction of intellectual capacity.

The care and management of infants with pertussis have undergone considerable change during the past two decades. No doubt our increased understanding of infant physiology has been a most important factor in the improved management of all diseases occurring during infancy. The fact that no fatal case of pertussis has occurred at The Infants' and Children's Hospitals in the past four years is probably significant, we feel, for reasons other than whatever value may be placed on serum therapy.

In this report little has been said concerning the prophylactic value of pertussis hyperimmune serum because we have had no experience with it. In several studies cited, the prophylactic value of the serum has been pretty clearly established.

SUMMARY AND CONCLUSIONS

1. An analysis has been made of 137 cases of pertussis in infants under 2 years of age admitted to The Infants' and Children's Hospitals between 1931 and 1945, forty-five of whom were treated with pertussis hyperimmune serum during the period 1941 to 1945.

2. The types of therapeutic procedures employed in the treatment of pertussis during the past fifteen years are reviewed.

3. It was not possible to prove or disprove the value of serum treatment from a study of such a small group of cases, although the case fatality rate has declined since its introduction.

The writer wishes to express his indebtedness to Dr. Charles A. Janeway, Dr. Gretchen H. Moll, and Dr. Jane Worcester for their assistance in the preparation of this report.

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STOOL EOSINOPHILIA IN GASTROINTESTINAL ALLERGY OF INFANCY

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MANIFESTATIONS of gastrointestinal allergy are quite frequent in infancy. The symptoms—colic, intermittent diarrhea, and retention-type vomiting—are so well known that the diagnosis is usually eventually made by the alert pediatrician, particularly if all the symptoms occur together or there is a convenient facial eczema to point an accusing finger. However, all these symptoms may have other causes: "Colic" may be due to anything from hunger or inept handling by the mother to hypersecretion and hypermotility calling for the use of antispasmodics; the diarrhea frequently suggests infectious diarrhea or even celiac disease; the vomiting is often indistinguishable in type from that of pylorospasm or pyloric stenosis. The long period of trial and error involved in making a differential diagnosis often leads to despair on the part of the mother and a change of doctors.

The desirability of a quick and easy method of spotting gastrointestinal allergies is, therefore, obvious. Such a method is available in the examination of the stool for the presence of eosinophiles.

Many years ago Haughwout[1] called attention to the presence of large numbers of eosinophiles in the stools of patients suffering from diarrhea caused by gastrointestinal allergy. This phenomenon has proved of considerable usefulness in the differential diagnosis of diarrheas.[2] It recently occurred to me that it would be worth while to look for eosinophiles in the stools of infants showing other symptoms suggestive of gastrointestinal allergy. The results have been very gratifying, as the following case reports will show.

CASE REPORTS

Group I. Simulation of Pyloric Stenosis

Case 1.—G. H., a female infant, was apparently normal at birth. She was fed on an evaporated milk mixture and gained 2 pounds in the first month. At 5 weeks of age she began to vomit with increasing frequency; vomiting was projectile in type and included large amounts of curdled milk, even when vomiting followed immediately after feeding. Stools were said to be normal. When she was seen at the age of 6 weeks her weight was the same as it had been at one month.

On examination there was visible gastric peristalsis, but no pyloric tumor was felt. Stools showed an excess of mucus, which, on staining, showed numerous eosinophiles.

Evaporated goat's milk was substituted for evaporated cow's milk in her formula. No other treatment was given. Vomiting promptly stopped, and eosinophiles were no longer found in the stool.

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Group II. Diarrhea and Vomiting

CASE 2.—G. V., a male infant, was first seen Jan. 24, 1948, at the age of 4 months with the complaint of vomiting and frequent small stools of three weeks' duration. Vomiting was projectile in type. The infant had been breast fed until the age of 3 weeks, after which he had been weaned to evaporated milk formula, on which he apparently did well until the onset of the present illness. Substitution of rice water for his formula controlled the symptoms, which recurred whenever milk was again given.

Examination showed moderate dehydration and a considerable degree of malnutrition (birth weight was 8 pounds and the weight at 4 months was 10 pounds 2 ounces). Stools showed an excess of mucus, which, on staining, was loaded with eosinophiles with a few pus cells.

He was put on a soybean formula (Mull-Soy) and a vitamin concentrate. Diarrhea and vomiting promptly stopped. When he was seen again in three weeks, his weight was 12 pounds, 5 ounces, and solid foods were added to his diet without recurrence of symptoms.

CASE 3.—B. L., a female infant, was seen at the age of 3 weeks with the complaint of vomiting and the presence of blood and mucus in the stools, following a shift from breast feeding to a cow's milk formula. Examination was normal except for the stools, which showed a large amount of bloody mucus which, on staining, was loaded with eosinophiles.

She was put on a soybean formula without improvement. The mother, on her own, then tried Olac and S-M-A without any change. Stools still showed many eosinophiles. She was then put on an evaporated goat's milk formula, after which all symptoms cleared. At the age of 10 months she was able to go over to a cow's milk formula without recurrence of symptoms.

Group III. Colic

CASE 4.—S. L., a female infant, was seen May 27, 1947, at the age of 12 days, with the complaint of violent crying after every feeding. Vomiting and diarrhea were not present. Examination was negative except for the stools, which showed numerous eosinophiles in the stained mucus. Formula was changed to Nutramigen with immediate relief of symptoms.

CASE 5.—R. K., a 2½ pound premature male infant, was under my care from birth. He had an uneventful hospital course, gaining well on an Olac formula and was discharged at the age of 2 months weighing 5½ pounds. As usual the undue amount of crying was not noted in the hospital. After one week at home the family was in a state of exhaustion, for the infant, while gaining well and not vomiting, "screamed from morning to night."

Examination was normal except for the stools, which contained an excess of mucus which was loaded with eosinophiles when stained. The formula was changed to Nutramigen, and all symptoms subsided.

Group IV. "Colic" and Diarrhea

CASE 6.—S. L., a female infant, was first seen Sept. 25, 1947, at the age of one month, with the complaint of excessive crying after feedings and frequent small mucoid stools. She had been bottle fed on an evaporated milk formula from birth. Examination was negative except for nasal obstruction and the presence of eosinophiles in the stools. The formula was changed to Nutramigen and subsequently to Mull-Soy without relief of symptoms. Eosinophiles persisted in the stool. On Oct. 24, 1947, she was put on evaporated goat's milk, and all symptoms were relieved.

CASE 7.—S. D., a female infant, was seen at the age of 2 months with the complaint that "she cried all day long," and had had a diarrhea for the preceding four days. She had been fed on almost every known brand of dried and liquid cow's milk without any improvement and had been given large doses of phenobarbital without relief.

Examination was negative except for the stools, which showed large amounts of mucus containing many pus cells and eosinophiles. It was felt she had both infectious diarrhea and gastrointestinal allergy. All symptoms cleared in forty-eight hours on a change to a goat's milk formula plus small doses of sulfadiazine, the necessity for which is debatable. This infant is still, at the age of 16 months, unable to take any form of cow's milk without a recurrence of diarrhea.

CASE 8.—C. T., a female infant, was first seen Feb. 4, 1948, at the age of 1½ months. She had been fed on an evaporated milk formula from birth and was doing well. Orange juice and cod liver oil were prescribed at that time.

Seen again on February 19, she was "crying all the time" and having frequent mucoid stools. Examination showed an early facial eczema and many eosinophiles in the stools.

A vitamin concentrate was substituted for the orange juice and cod liver oil. This resulted in prompt clearing of symptoms and disappearance of eosinophiles from the stools.

Group V. Simulation of "Celiac Disease" and Fat Intolerance

CASE 9.—K. M. was first seen Sept. 25, 1947, at the age of 4 months, with the complaint of frequent, large, pale bowel movements and failure to gain weight. The symptoms had been present with gradually increasing severity since the age of one month. The infant had been bottle fed since birth. Stools were said to be normal when skimmed milk was fed, but there had been no weight gain for one month. There was no colic or vomiting.

Examination showed an undernourished infant with a protuberant, gassy belly. Stool (even on skimmed milk) was pale, foamy, and loaded with fatty acids and neutral fats. The findings were so apparently typical of celiac disease that *no stain for eosinophiles* in the stools was made, and treatment was confidently started with crude liver extract and fat-free diet.

The usual dramatic response failed to appear: After three weeks the stools had not changed and only 8 ounces of weight had been gained. At this time the

stool was first examined for eosinophiles, and they were found in large numbers in the mucus. The formula was changed to goat's milk without improvement or weight gain after one week. Numerous eosinophiles were still present in the stool. A change to Mull-Soy brought immediate improvement; eosinophiles and excess fats and fatty acids disappeared from the stools in two days, and a weight gain of 2 pounds occurred in two weeks. The subsequent progress (age now 10 months) has been normal.

CASE 10.—P. A., a female infant, bottle fed from birth, was first seen Jan. 21, 1948, at the age of 5 weeks. The complaint was of poor weight gain. The weight was 8 pounds, as compared with a birth weight of 7½ pounds. Stools were said to be normal. The formula was an extremely dilute evaporated milk mixture, and it was felt that the failure to gain was explained by an insufficient caloric intake. An adequate evaporated milk formula was prescribed. Seen one week later the infant was gaining poorly, and stools were pale and mushy, showing an excess of fatty acids. On a diagnosis of "fat intolerance," the formula was changed to Dryco. A good weight gain followed: On March 1 the weight was 11 pounds, 13 ounces, and stools were said to be "frequent, but of good color."

By March 10 this frequency had increased to eight to ten daily, and the weight gain had stopped. Stools were for the first time examined for eosinophiles, and they were found in large numbers. The formula was changed to evaporated goat's milk, and within two days the stools were normal in number and free of eosinophiles and excess fats.

CASE 11.—M. F., a male infant, was seen in consultation at Children's Hospital at the age of three months, with a history of large, frequent, loose stools and failure to gain weight. He had been a "feeding problem" from birth, with a tendency to diarrhea on the many formulas (all derived from cow's milk) which had been tried.

Stool examination in the hospital had shown great excess of fats and fatty acids, and a diagnosis of celiac disease had been made. No response was obtained from parenteral liver extract, large doses of B-complex, and a fat-free formula.

On examination he was only one pound over birth weight (8½ pounds), was markedly undernourished, and had a protuberant, gassy abdomen. The stool showed massive numbers of eosinophiles in the stained mucus.

A diagnosis of gastrointestinal allergy was made, and the use of a Mull-Soy formula was suggested. Within three days the diarrhea was controlled, and within two weeks he had gained 2 pounds.

DISCUSSION

These illustrative cases have been selected from over thirty patients in my practice in the past two years who have shown eosinophilia in the stools. They represent a group of patients who are frequently found in any pediatric practice. I believe the diagnosis in all the cases would have been made eventually without examining the stools for eosinophiles, but in the majority a long period

of trial and error was eliminated. In the three patients in Group V, a great deal of grief for doctor and patient could have been avoided by looking for stool eosinophiles on the infant's first visit.

TECHNICAL DATA

Beautiful preparations to demonstrate eosinophiles in stools can be made by wet fixation of films of mucus in Schaudinn's solution and staining with Giemsa. However, this method is time-consuming and requires equipment not available in every doctor's office. A satisfactory, rapid method is as follows:

1. Stool specimen is generally obtained by inserting a gloved finger into the infant's rectum; the "suppository" action will usually produce enough material for examination.
2. Mucus is carefully picked free of stool material with fine forceps and placed on a glass slide.
3. A cover slip is dropped on the mucus and the preparation examined under the microscope to determine whether cells are present.
4. If cellular material is present, a film is made by gliding the cover slip off the slide.
5. The slide is then immediately heat-fixed over a flame.
6. Wright's stain is flooded onto the slide while it is *still hot*, and immediately diluted with water or buffer solution.
7. Allow to stain until the surface of the liquid is covered with a greenish opacity.
8. Wash, dry over a flame, and examine under cedar oil. The entire process takes less than five minutes.

CONCLUSION

Examination of the mucoid portion of stools for the presence of eosinophiles is of value in recognizing gastrointestinal allergy in infants.

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THE TREATMENT OF EPIDEMIC VOMITING IN PEDIATRIC PRACTICE

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VOMITING is a common initial symptom in the acute infectious diseases of children. This is particularly true in diseases of the respiratory tract. However, cases are often encountered in which it is difficult to find any evidence of infection that is responsible for the vomiting.

In Baltimore and its environs it has been the experience of pediatricians and general practitioners of medicine to see individuals who repeatedly vomit for twenty-four hours or longer without exhibiting any positive physical findings. The syndrome, while most prevalent in children, also occurs in adults, but seldom occurs in infants under 6 months of age. It has a rather striking seasonal incidence, being seen almost entirely during the months of October and November, and then disappearing with the onset of seasonably cold weather. However, when the weather is unseasonably warm, it will continue through December and January or until the appearance of cold weather.

The onset is quite abrupt. A previously well child will suddenly begin to vomit, usually with no preceding complaint of nausea. The patient then continues to vomit at frequent intervals. An associated retching is seen in those individuals who are emotionally of high timbre. All of the patients have an insatiable thirst and constantly crave water, which, when given, is promptly vomited. The vomiting, as a rule, subsides within twenty-four hours, with, in the main, no aftermath other than a slight indisposition and anorexia lasting for several days. During the fall and winter of 1946-1947, respiratory infections seemed to follow the onset of vomiting in about seven days. These were manifested by a rather severe tracheobronchitis of stubborn duration and very often a complicating otitis media. This was so constantly observed that the connection between vomiting and respiratory infection seemed an inevitable conclusion. However, in other years, no connection could be established with any subsequently appearing respiratory infection.

The infectiousness of the disease is well illustrated by the rapid appearance of vomiting within twenty-four to forty-eight hours in other members of the family.

Abdominal pain is often encountered and is localized by the patient in the left quadrant. It is fleeting in type and not too severe. The umbilicus is also given by many children as the site of the pain.

Diarrhea is usually not associated with the vomiting. The stools, seldom numbering more than three per day, are light in color, almost white, and have an extremely foul odor. The odor disappears in several days with appropriate dietary measures, but the color persists for four or five days.

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The temperature is seldom elevated beyond one or two degrees and in the majority of cases is usually normal. Those who have an elevation of temperature maintain it for only twenty-four or forty-eight hours.

Physical examination is completely and entirely negative. Transient glycosuria causing a trace to three-plus reduction is seen in the majority of patients.

The blood findings are not remarkable. There is usually a slight reduction in the total number of leucocytes, with a relative increase in the granulocytes. Reimann and his associates,[4] however, reported leucocytosis in their series.

While most of the cases are of short duration, there are occasionally some that seem to be prolonged. The following are three cases that seemed to have had their origin with the vomiting previously described:

CASE REPORTS

CASE 1.—B. G., aged 3 years, was seen on Jan. 3, 1942, because of occurrence of glycosuria, found on repeated examinations by her family physician. In November of 1941, the child had a period of vomiting for forty-eight hours. Following the cessation of vomiting, she complained of vague abdominal pain, developed marked anorexia, frequently complained of nausea, and on several occasions vomited. It was also noticed that the stools were very pale in color and of particularly foul odor. A low-grade fever seemed to persist for several weeks. Physical examination through this period and at the time of admission was essentially negative. It was felt advisable that this child be admitted to the hospital for study. The results were as follows:

Urinalysis showed a three-plus sugar on only two occasions, and both of these were on nonfasting specimens. All fasting specimens were negative for sugar. Nonprotein nitrogen determinations were 25 and 34 mg. per cent on two occasions. The blood amylase gave a reading of 142. The results of the glucose tolerance test were as follows:

Fasting blood sugar	74 mg.
½ hour	164 mg.
1 hour	278 mg.
2 hours	264 mg.
3 hours	180 mg.
4 hours	155 mg.

The urine specimens collected gave a two-plus reduction test at the first, second, and third hours. The blood count was essentially normal, with a hemoglobin value of 14 Gm., and with leucocyte and differential counts giving entirely normal values.

The patient, who had been on a restricted carbohydrate diet, was placed on a high thiamin chloride, low fat, low residue, high carbohydrate diet, with tincture of belladonna, minims 5, t.i.d., a.c., and discharged. The child's appetite improved, the stools returned to normal, and she seemed quite well within three weeks. At the end of six weeks, after repeated urinalyses had failed to show the presence of sugar, other than one plus following meals, the glucose tolerance test was repeated and the curve found to be within normal limits. This patient has continued quite well.

CASE 2.—M. H., 5 years old, was referred because of anorexia and the frequent occurrence of glycosuria of three months' duration. She was first seen in March of 1942. Further history added only the presence of low-grade fever for three weeks following the onset of an episode of vomiting of forty-eight hours, and it was noted that the mother, father, and an older sister also had vomiting at this time. This was attributed by the parents to some dietary indiscretion. Following the vomiting, it was then noted that the anorexia and glycosuria occurred. The patient was admitted to the University Hospital for observation. The results of the hospital study were as follows: Repeated examination of fasting urine specimens gave a one-plus reduction for sugar. The glucose tolerance test was as follows:

Fasting blood usgar	80 mg.
½ hour	155 mg.
1 hour	200 mg.
2 hours	196 mg.
3 hours	170 mg.
4 hours	130 mg.

The collected urine specimens showed the fasting urine to have no sugar, but the one- and two-hour specimens gave a two-plus reduction; the others were negative. The blood amylase was 154 in this patient. Other findings were noncontributory. The patient was discharged on a high thiamin chloride, low fat, high carbohydrate, low residue diet, with pancreatic extract, grains 5, t.i.d., a.c. The patient was seen again in six weeks, her appetite had improved, and for the last four weeks there had not been any glycosuria. A repeated glucose tolerance was done at this time, and the curve found to be perfectly normal.

CASE 3.—R. B., 16 months old, began to vomit following the other members of the family. Despite all medication, the vomiting persisted, and the infant was seen by me on Dec. 18, 1942. Physical examination demonstrated only a markedly dehydrated infant with a temperature of 103° F. The patient was hospitalized at the University Hospital. The admission blood sugar was reported at 284 mg. Before the blood sugar was reported, 250 c.c. of 10 per cent glucose had been given intravenously. The following morning the blood sugar level was 78 mg. The subsequent course was uneventful, and the patient was discharged on Dec. 24, 1942.

These cited cases seem to have had their onset as a result of infectious vomiting. The temporary derangement of carbohydrate metabolism is interesting and it would have been quite simple to have diagnosed the first two cases as low-threshold diabetes, had it not been subsequently determined by course and blood sugar check to be otherwise. Unfortunately, biochemical studies have not been made on the majority of patients with epidemic vomiting, for they, as a rule, promptly recover.

Many of the cases of epidemic vomiting are considered by parents to be purely the result of faulty food intake, a conclusion they derive from the fact that all members of the family are affected with the same malady. This makes it difficult to give any accurate estimate as to the frequency of actual occurrence. However, I have accumulated, from private practice, a total of 773 cases as shown in Table I. This figure shows that the disease is very frequent, and also as gathered from the table, that it makes a fairly constant yearly appearance.

TABLE I. OCCURRENCE OF EPIDEMIC VOMITING IN 773 PATIENTS

YEAR	NUMBER OF CASES
1940-41	103
1941-42	96
1942-43	109
1943-44	167
1944-45	126
1946-47	182
Total	773

The case of epidemic vomiting as seen in the child, if treated properly responds promptly and need not occasion any alarm. Restriction of fluid by

mouth in large quantities is necessary because, if given, it is promptly vomited. While Brennemann[5] states that fluid by mouth which is eventually vomited is useful in washing out the stomach, it also creates an unnecessary chloride loss. A high carbohydrate intake is desirable. The frequently advocated orange juice fortified with sugar is not tolerated. Lollypops or all-day suckers are occasionally found to be of some help. Sedation obtained by the use of paregoric or phenobarbital is generally not of any value.

The treatment that I have found without exception to be satisfactory is as follows:

Coca-Cola syrup (obtained at the drugstore fountain) is given in teaspoonful doses at intervals of fifteen to thirty minutes until three or four doses have been retained. Nothing other than the Coca-Cola syrup is permitted. This must be stressed to the parent. Usually, there is no further vomiting after the first dose of Coca-Cola syrup. Then, one teaspoonful is given every three hours for the next forty-eight hours. Following the initial treatment with Coca-Cola syrup, the patient is then permitted such foods as apple sauce, gelatin products, precooked cereals with only added sugar, toast or crackers, and jelly. The only fluids permitted for the remainder of the twenty-four hour period are tea, cracked ice, and very small, frequent sips of water. After the initial twenty-four hour period of treatment has been completed, additions to the diet then consist of skimmed milk, fruit juices, with the exception of orange juice, cooked cereal, strained broth, and baked potato. The continuation of a low residue, low fat, high carbohydrate diet is advisable for at least four days after the onset of the vomiting.

The preceding treatment will be found to be very satisfactory and, if used as outlined, will give uniformly prompt results. I have tried all of the suggested treatments as given by various authorities for the treatment of vomiting and have found no other to be as practically useful as this one. I can only speculate as to why the Coca-Cola syrup is effective in the control of vomiting. It must be the xanthine content that is primarily responsible by its effect on the smooth muscle of the stomach. Therapeutic doses of the xanthines have no significant effect on gastric activity. However, high concentrations do depress the tone and amplitude of contractions of isolated intestinal strips, so it would seem not unlikely that the Coca-Cola syrup reduces the gastric tone. This may explain its effectiveness in the control of vomiting.

The syndrome is called by a variety of terms, the most common being "intestinal flu." The literature is replete with descriptions of seasonal emesis under such terms as seasonal gastroenteritis,[1] Spencer's disease,[2] and acute infectious gastroenteritis.[3] Reimann and his co-workers[4] reported extensively upon "epidemic diarrhea, nausea and vomiting of unknown cause," which occurred in the Philadelphia area in the fall of 1943 and again in 1944. Their attempts to determine an etiological agent were fruitless. Finkelstein is quoted by Brennemann[5] as speaking of Beech epidemic or epidemic of vomiting. Brennemann[5] himself speaks of vomiting only in association with evident infectious diseases. Whether it is a distinct entity or not will be determined only through biochemical and bacteriologic studies. However, at the present it seems appro-

priate to recognize a disease that is characterized by vomiting and low-grade fever, with occasional temporary carbohydrate disturbance, and one that is infectious. Therefore, until many findings are clarified, the term "epidemic vomiting" seems appropriate for this syndrome.

SUMMARY

1. A report of 773 cases of an infectious type of vomiting is given.
2. A definite clinical entity is assumed.
3. It is of very frequent occurrence in private practice of pediatrics.
4. The successful control of the vomiting with the use of Coca-Cola syrup is described.

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TORSION OF THE SPERMATIC CORD IN THE NEWBORN INFANT

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TORSION of the spermatic cord, or, as commonly designated, torsion of the testicle, is an axial rotation of the testicle and epididymis or, as in the cases here reported, of the entire scrotal contents with a cutting-off of the blood supply. Unrelieved, this results in hemorrhagic infarction of the strangulated structures and, if infection exists, suppurative gangrene. The disease is predominantly one of the later years of childhood and the earlier years of adulthood; O'Conor[1] found the average age incidence to be 13 years and 4 months. Yet the occasional observation of unilateral atrophic testis in boys with a classical history of torsion years previously suggests that the condition occurs sufficiently often to demand its diagnostic consideration when acute scrotal swelling occurs in the newborn or young infant.

The earliest record of this condition in the newborn infant is that of Taylor,[2] in whose patient the acute condition was noted when the boy was 4 hours old. Trillot[3] encountered it in a 3-day-old male, and others have recognized it in subsequent months. Allen and Andrews[4] had three cases at Bellevue Hospital in infants under 12 months of age. Donovan[5] collected 163 cases, of which thirteen were in children under one year of age. My two cases are apparently the second and third to be reported in which the torsion occurred during the first day of life. They were necessarily treated by castration on the third and seventeenth days of age respectively. Moreover, these two cases are of special pathologic interest because the torsion occurred outside the tunica vaginalis (Figs. 1 and 2)—a condition denied by many to occur.

ETIOLOGY AND PATHOLOGY

Torsion of the spermatic cord occurs more often on the right side, and in about 5 per cent of the reported cases has been bilateral. The torsion can occur in either direction and even through two or more complete turns. The direct cause of torsion of the spermatic cord is unknown, and the usual hypothesized factors concerned with its occurrence in older patients probably do not hold during the neonatal period. In older patients, the genesis of the condition has been attributed to a variety of conditions which afford unusual testicular mobility, and are chiefly maldescent, lack of a gubernaculum, lack of attachment to the tunica vaginalis, anomalous formation, or undue spaciousness of the tunica vaginalis. Sudden strain and/or spontaneous contraction of the cremasteric muscle is believed to bring about the twist, in some unknown way. Yet in many instances the torsion has occurred during sleep. In about 500 reported cases (thirty in my experience) there has been an anomalous development, predominantly of the testicle-epididymis relationship, and characterized in the main

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by an unusually long mesorchium. In many of these, the testicle previously had been observed to be abnormally mobile or imperfectly descended. Yet in the newborn infant with extratunical torsion and with the possible exception of testicular maldescent, these anatomic explanations defy practical clinical consideration.

When the condition occurs in older patients, the site of the torsion is regularly within the tunica vaginalis, but in Taylor's case[2] and in both of mine, the twist occurred outside of the tunica vaginalis (Figs. 1 and 2). This observation affords special etiological interest and clinical distinction. Long ago Sir Ashley Cooper noted that the entire scrotal contents of the newborn infant could be freely lifted out of the scrotum without tearing of tissue, and this explains how torsion including the tunica vaginalis can occur. Presumably cremasteric contraction is the impelling force producing the twist. In mild torsion with incomplete shutting-off of the blood supply, the late result is mild atrophy of the testicle. In complete and unrelieved strangulation, the testicle and epididymis proceed to hemorrhagic gangrene, subsequent atrophy, and isolateral sterility. Occasionally the testicle disappears entirely. Microscopically, the testes and epididymis show extensive hemorrhagic necrosis with widespread red blood cell infiltration. The late picture is that of advanced universal fibrosis with corresponding loss of spermatic and tubular elements. Even with prompt detorsion, some atrophy usually follows.

SYMPTOMS

The usual onset of torsion of the spermatic cord is sudden with excruciating pain in the testicle, which may be referred to the inguinal region, over the iliac crest, or to the abdomen. Gastrointestinal disturbances, notably nausea and vomiting, generally occur and, when the testis is improperly descended, may suggest incarcerated inguinal hernia. When the testis is in the scrotum there is pronounced painful swelling of the involved side, but this is localized to the scrotum. The condition may simulate orchitis, epididymitis, torsion of the testicular appendage, strangulated hernia, or, in the newborn infant, hemorrhagic infarction of the testicle. With complete infarction due to torsion, the testicle ultimately may become nearly insensitive. The systemic manifestations are those common to toxemia, although fever is low or absent.

DIAGNOSIS

The sudden onset of acute scrotal swelling in a young person without urogenital infection at once suggests the diagnosis of torsion of the spermatic cord. The prostate will feel normal. Acute hydrocele may preclude differentiation between epididymis and testicle, and sanguineous fluid in the tunica vaginalis will prevent transillumination. When the upper end of the epididymis is involved in the twist, palpable swelling of the tender peripheral segment of this organ will suggest epididymitis. In torsion, the scrotal skin is less likely to be adherent to the underlying structures than it is in acute epididymitis. Prehn[6] observed that elevation of the involved testicle relieves the acute pain of epididymitis but not of torsion. In newborn infants the acuity of the pain is such

that they obviously do not wish to move, to be moved, or to have their genitalia handled. If the testicle is undescended in the inguinal canal, the acute manifestations are localized to the groin, and in the rare instances of torsion of an intra-abdominal testicle, the diagnosis of acute surgical intestinal disease is generally made. Recently in a 5-month-old boy with right undescended testicle and acute swelling near the internal inguinal ring, the clinical manifestations made the diagnosis of torsion of an undescended testicle seem unquestionable. Yet exploration disclosed strangulated hernia with inclusion of the undescended testicle in the acute fibrinous reaction. Reduction of the hernia, fortunate restoration of circulation of the strangulated 6-cm.-long loop of gut, and fixation of the testicle in the lower scrotum were curative.

In torsion of the spermatic cord the white blood count is generally under 15,000 and rarely over 20,000 cells per cubic millimeter, but the polymorphonuclear count will be elevated to 60 to 90 per cent.

TREATMENT

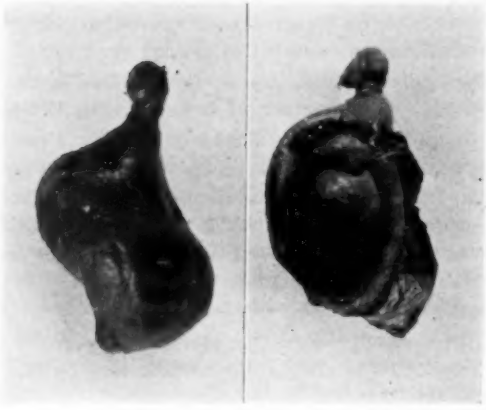
If the patient can be operated upon within four hours after the acute onset surgical detorsion will usually conserve the organ. Yet partial testicular atrophy may be expected to reflect the damage caused by the temporary strangulation of the spermatic cord. In a few instances spontaneous detorsion has occurred, and in others prompt manual untwisting has relieved. Unfortunately most patients with torsion are treated for days with ice caps, coal-tar analgesics, and vain hope, so that with the usual delay castration is demanded. When the opposite testicle is abnormally mobile, it should be fixed to the lowermost scrotum to prevent subsequent torsion on this side, as I have observed to occur in two young men, one of whom thereby became a eunuch. In Case 1, to be described, the surgical treatment was carried out, under local anesthesia, when the child was 3 days old.

CASE REPORTS

CASE 1.—R. G. was delivered by normal birth on June 2, 1946. Twenty-four hours post partum his nurse noticed the right scrotum was swollen and apparently tender. On the third day I saw the child in consultation and found the right scrotum swollen to approximately four times normal size. The overlying skin was edematous and firmly attached to the underlying structures, and acute hydrocele precluded deep palpation. At the upper pole of the scrotum the cord was tender and thickened, but not at its entrance to the external inguinal ring. Temperature was normal.

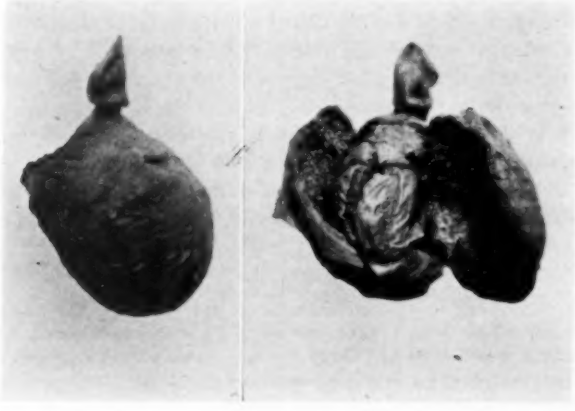
The blood count was as follows: hemoglobin 19.5 mg. (130 per cent); red blood cells 5.46 million; white blood cells 15,850; polymorphonuclears 89 per cent; lymphocytes 9 per cent; myelocytes 2 per cent. There was a severe shift (Schiller) to the left and mild toxic granules.

A diagnosis of torsion of the spermatic cord was made. Without delay and under local anesthesia, using 0.5 per cent novocain hydrochloride solution, the scrotum was opened. The tunica vaginalis was found tensely distended and blue. On opening it, about 2 c.c. of bloody hydrocele fluid gushed forth, and the testicle and epididymis were each found enlarged about three times and mahogany color. Further examination disclosed a clockwise torsion of the spermatic cord of 180 degrees just outside the tunica vaginalis (Fig. 1); the spermatic cord above this point was normal. Orchidectomy was performed. Convalescence was uneventful, and the child was discharged home with his mother one week later.



A. *B.*

Fig. 1.—*A.* Torsion of the spermatic cord in Case 1 showing twist outside (above) the tunica vaginalis. *B.* Hemorrhagic infarction of involved structures. Note 180 degree twist of cord at upper pole as well as the great swelling of the epididymis and thickening of the tunica vaginalis.



A. *B.*

Fig. 2.—*A.* Torsion of spermatic cord in Case 2 with twist outside tunica vaginalis. *B.* Because of infection and greater duration of the condition, the indurated tunica vaginalis is six times normal thickness. The epididymis is gangrenous, as is the shrunken testicle.

CASE 2.—J. L. On May 3, 1947, I was called in consultation to see this 17-day-old boy who presented a hard, right scrotal swelling about 3 by 2.5 cm. and with an obvious abscess measuring 1.5 by 1.5 cm. at the lower scrotal pole. There was marked scrotal redness together with mild inguinal lymphadenitis. The testicle and epididymis could not be differentiated, and the lower half of the scrotum was adherent to the underlying structures. At its entrance to the external inguinal ring the spermatic cord was normal. Rectal examination was negative. The history was elicited that the day after birth a swelling of the right scrotum was noted, but received no attention other than wet dressings until the sixth day when the family physician, an osteopath, thought the boy might have a tumor of the testicle. An aspiration biopsy was performed, which apparently succeeded only in introducing infection and which ultimately

resulted in the previously described lower polar scrotal abscess. Eventually a pediatrician, Dr. William Matthews, was called in consultation, and he in turn called me; a tentative diagnosis of torsion of the spermatic cord was made.

The child was taken at once to the hospital (the age then 17 days). The red blood cell count was 4.13 million; hemoglobin 11.6 Gm. (77.3 per cent); leucocytes 20,000, with 61 per cent polymorphonuclears and 39 per cent lymphocytes. Under open drop ether anesthesia the right scrotum was opened with a racquet-shaped incision which excised the necrotic lower scrotal pole and liberated about 2 c.c. of pus. The local pathologic change was a duplication of that described in Case 1 except that hemorrhagic gangrene of the testicle and epididymis was more advanced and the tunica vaginalis was greatly thickened. Likewise, the twist was extravaginal just above the point of attachment of the tunica vaginalis to the spermatic cord, and of a slightly greater degreé than in Case 1 (Fig. 2). Orchidectomy was performed, and the scrotum was closed about a small Penrose drain. Convalescence was uneventful, afebrile, and the infant was discharged home three days later.

SUMMARY

Attention has been directed to the occurrence of torsion of the spermatic cord during the first day of life in two cases and terminating in loss of the testicle. In each instance, the twist occurred outside the tunica vaginalis. If the condition is recognized and detorsion can be performed during the first four hours, the testicle usually can be preserved. Diagnostic and therapeutic delay means loss of the organ.

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CALCIFIED INTRACRANIAL TUBERCULOMAS

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INTRODUCTION

THOUGH tuberculomas of the brain have been observed less frequently in recent decades, their clinical recognition and occurrence in autopsy material is not uncommon. Wilson and Bruce,[1] in a collective review of recent statistics, concluded that intracranial tuberculomas constitute 3.6 per cent of verified brain tumors. Nearly half of the tuberculomas of the brain have been encountered in patients under 10 years of age,[2] indicating that this condition is of relatively greater importance during childhood. Calcification in these lesions has been described as an apparently infrequent phenomenon. Scott and Graves,[2] in a review of 815 cases of intracranial tuberculomas, noted calcification in only eleven cases. In a recent survey by Weinberger and Grant[3] in 1942, nineteen verified cases of calcified intracranial tuberculomas were collected from the literature, to which the authors added one case of their own. Since publication of this paper, I have been able to find three additional cases in the literature.[4, 5]

This rare occurrence of calcified tuberculomas of the brain is surprising, considering the fact that calcification is not an uncommon event in tuberculous lesions of other organs. It has been suggested that some of these lesions may remain unrecognized during life in the absence of roentgenographic studies.[6]

Cerebral tuberculomas have received renewed interest, since it has been shown that surgical procedures in this condition are not necessarily followed by fatal meningitis but may prove to be of therapeutic value in selected cases.[7] This should apply particularly to calcified or ossified lesions in which a tendency towards healing and encapsulation is conspicuous. It remains in the realm of speculation whether with advances of antibiotic therapy, healing and calcification in cerebral tuberculomas will occur more frequently, making it feasible to recognize them on roentgenologic examinations. From the diagnostic standpoint, calcified tuberculomas of the brain are of importance since they present roentgenologic features which, in many instances, permit their differentiation from other calcifying intracranial lesions.[3]

For these reasons, it was considered of interest to record the following cases of calcified intracranial tuberculomas observed in childhood.

CASE REPORTS

Case 1.—J. H., a 20-month-old Negro orphan girl, was admitted in September, 1943, because of pain and swelling of the left leg. Roentgenograms of the distal tibia revealed an oval-shaped cystic area of rarefaction, which was surrounded by slight bone sclerosis and extended into the epiphyseal plate. This process was interpreted as chronic osteomyelitis. Histologic examination of biopsy material from this lesion disclosed the presence of tuberculous granulation tissue and acid-fast organisms. Roentgenograms of the chest revealed calcium deposits in the right lower lung field and calcified mediastinal lymph nodes, but no definite active lesions in the lung parenchyma (Fig. 1). On a search for further bone lesions, roentgenograms of the skull were obtained, and a moderate number of small, serrated and

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angular, calcareous deposits were discovered in the cranial cavity (Fig. 2). These lesions were believed to represent intracranial tuberculomas.

There was considerable clinical improvement during the hospital stay. The patient was discharged in November, 1943, and subsequently seen on several occasions in the outpatient department.

In January, 1945, the child became suddenly ill with abdominal pain, nausea, and vomiting. On physical examination after hospital admission, she was found to stay on her side in a semicomatose condition with her legs and thighs flexed. The neck was stiff, and Kernig's and Brudzinski's signs were present. There were no remarkable chest findings, but the cervical lymph nodes were found to be enlarged bilaterally.

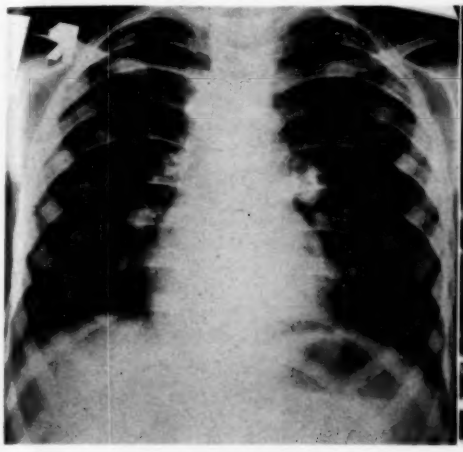

Fig. 1.

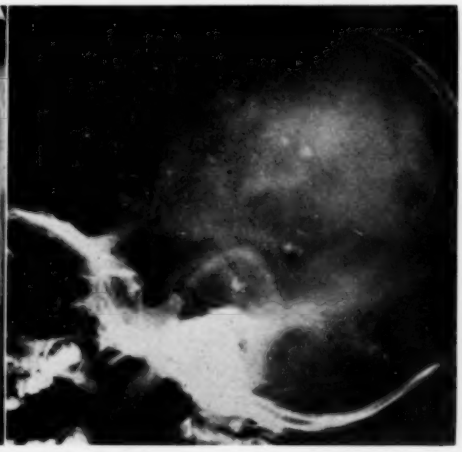

Fig. 2.

Fig. 1.—Case 1. Extensive calcification of mediastinal lymph nodes and calcium deposits in right lower lung field.

Fig. 2.—Case 1. Multiple intracranial tuberculomas. Note irregular and serrated contour of the lesions.

The laboratory findings showed a normal red blood cell count and slight leucocytosis. The urine examination showed a few pus cells per high power field. The spinal fluid appeared clear and contained 1,168 white blood cells per cubic millimeter, with 98 per cent lymphocytes and 2 per cent polymorphonuclears. Smears of the spinal fluid did not disclose acid-fast organisms. The spinal fluid sugar was found to be 49 mg. per cent. A first-strength tuberculin test was positive.

After a rapid downhill course the patient died on the fifth hospital day.

Essential Autopsy Findings.—Pleural adhesions were noted over both pulmonary apices. The tracheobronchial lymph nodes appeared enlarged, and one lymph node in the left hilum revealed extensive caseation. Calcium deposits were noted in both lungs and hilar lymph nodes. The heart, liver, pancreas, and kidneys were grossly not remarkable. The spleen contained several small yellowish nodules. The mesenteric lymph nodes were considerably swollen, but there was no caseation found on cut section. The brain weighed 140 Gm. The cerebrospinal fluid appeared cloudy and was increased in amount. The base of the brain was covered by a large amount of thick, gelatinous, greenish exudate, which extended laterally towards the sylvian fissures. Cut sections of the brain after fixation disclosed eleven calcified lesions in the gray and white matter of the cerebrum, the floor of the posterior horn of the right lateral ventricle, the pons, and the cerebellum. Histologic examination of the brain confirmed the gross anatomic diagnosis of tuberculous meningitis. The calcified masses were found to represent tuberculomas, varying in appearance from fibrosis to obvious activity.

Comment.—A 20-month-old child with pulmonary and osseous tuberculosis was found to have on roentgenographic examination multiple calcified intracranial tuberculomas. The child remained free of cerebral symptoms for a period of observation of fifteen months, then developed fatal tuberculous meningitis. On autopsy, eleven calcified tuberculomas of the brain in various stages of activity were found.

CASE 2.—C. S., a 15-month-old Negro boy, was admitted on Aug. 2, 1945, because of recent lye burns of the lips, mouth and throat. On physical examination, numerous coarse and fine moist râles were heard over both lungs, and dullness was noted over the upper two-thirds of the right lung. The cervical and axillary lymph nodes were found to be enlarged. There were no unusual urinary findings, and the red blood count was within normal range. The white blood count disclosed 25,000 leucocytes with 1 per cent eosinophiles, 42 per cent polymorphonuclears, 56 per cent lymphocytes, and 1 per cent monocytes. The first- and second-strength tuberculin tests were negative. Roentgenographic examination of the chest two days after admission disclosed an extensive, rather homogeneous consolidation in the region of the right upper and right middle lobes. Aspiration pneumonia was considered likely, and the patient was treated with penicillin and sulfadiazine. This was followed by improvement in the general condition of the patient and satisfactory healing of the burns.

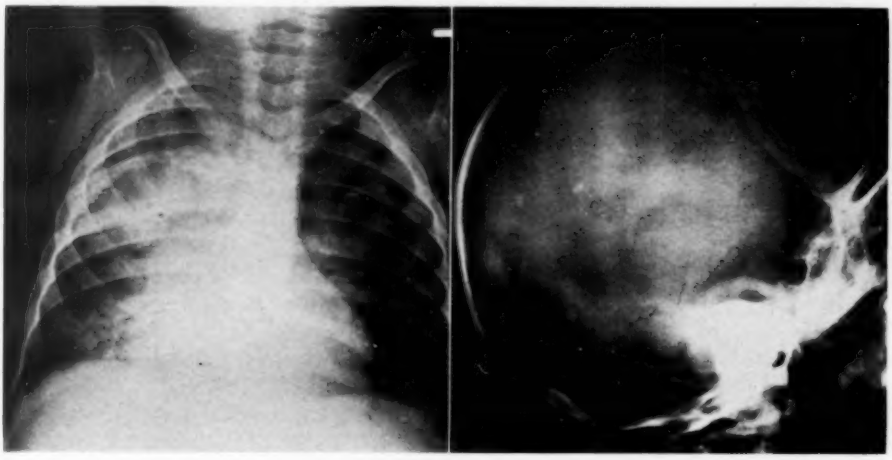

Fig. 3. Fig. 4.

Fig. 3.—Case 2. Tuberculous osteomyelitis of right fifth rib. Tuberculous infiltration of right lung and extensive lymphadenopathy.
Fig. 4.—Case 2. Four calcified tuberculomas in posterior portion of cranial cavity.

After discharge from the hospital, the patient was seen on several occasions in the out-patient department. He was readmitted on March 1, 1946, because of extensive swelling of the neck. The temperature on this second hospital admission was 103° F., the pulse rate was 120, and the respirations were 28. The cervical lymph nodes were markedly swollen, and a hard, nonfluctuant mass was palpable in the region of the right mandible. Inspection of the mouth revealed several draining sinuses on the buccal surface of the right cheek and base of the tongue. A firm swelling about 3 cm. in diameter was noted in the posterior chest wall in the region of the fifth rib.

The laboratory studies on this admission revealed a strongly positive first-strength tuberculin test. The blood count was not remarkable.

Roentgenograms of the chest revealed an extensive consolidation throughout the right hilar area and right lower and intermediate lung fields, where there were several small calcium

deposits. The inferior aspect of the posterior portion of the right fifth rib showed an oblong area of destruction, surrounded by a large soft tissue mass (Fig. 3). There was no significant bone proliferation in this region. Roentgenograms of the mandible disclosed almost complete destruction of the right angle, with formation of numerous small sequestra. The roentgenologic examination of the skull disclosed four serrated calcium deposits, measuring approximately 5 mm. in diameter in the right parieto-occipital area of the brain (Fig. 4).

The presence of tubercle bacilli in the gastric contents was proved by guinea pig inoculation.

During a hospital observation of nine months, no remarkable changes in the patient's condition were noted. His temperature usually fluctuated between 99° and 103° F. Following discharge from the hospital the patient's family moved to another city. It was learned that he died in June, 1947. The exact circumstances of his death could not be ascertained.

Comment.—A 2-year-old child with pulmonary and osseous tuberculosis was found to have four calcified intracranial tuberculomas. There was no history of any symptoms referable to the central nervous system, nor did the patient develop any signs of intracranial disease during an observation of nine months. Though the calcified lesions of the brain cannot be considered proved tuberculomas, this diagnosis is highly probable in the presence of typical roentgen findings and active tuberculosis of the lungs and bones.

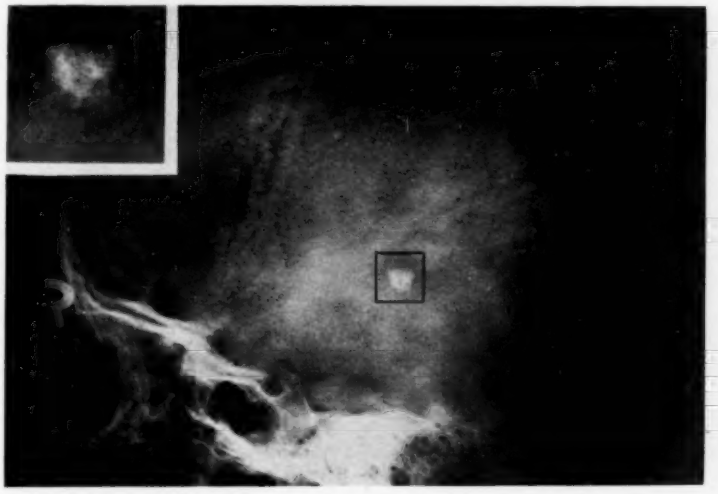

Fig. 5.—Case 3. Solitary calcified tuberculoma.

CASE 3.—H. R., a 9-year-old white boy, sustained a head trauma on Feb. 2, 1948. Following the accident, he vomited twice and developed some drowsiness. The neurological findings on admission were entirely negative. Rapid improvement of the patient's condition permitted an early discharge from the hospital.

Roentgenologic examination of the skull did not disclose any fracture lines or depressed fragments, nor were there signs of increased intracranial pressure. There appeared, however, in the right parietal area, 10 mm. to the right of the midline, an oval-shaped serrated calcium deposit measuring 7 by 10 mm. in diameter (Fig. 5). A chest roentgenogram disclosed calcium deposits in the left hilar area and linear densities in the left intermediate lung field resembling pulmonary scars.

At the age of 12 months the patient had been diagnosed as having childhood tuberculosis, on the basis of a chronic pulmonary infiltration, cervical lymphadenopathy, and positive tuberculin tests. His father was known to have active pulmonary tuberculosis at that

time. At the ages of 3 and 5 years, he was known to have had a number of convulsions. Otherwise, his physical and mental development had been satisfactory under the guidance of a tuberculosis clinic. At the time of hospital admission, he was considered to have arrested pulmonary tuberculosis.

Comment.—In a 9-year-old boy, a calcified intracranial mass was recognized roentgenologically as an incidental finding. The history of childhood tuberculosis, as well as the characteristic roentgenologic findings, make it very likely that the observed intracranial calcified mass represents a tuberculoma which was apparently asymptomatic at the time of observation.

Fig. 6.—Post-mortem roentgenogram of brain (Case 1). Note the serrated and angular appearance of the calcified tuberculomas.

ROENTGENOLOGIC FEATURES

Calcified tuberculomas of the brain may vary greatly in size and number. The calcium deposits in these lesions measure usually from a few millimeters to 2 to 3 cm. in diameter.[3] Though most of the lesions have been described as solitary, multiple lesions have occurred in a smaller number of cases.[2] Thus, Borchardt[5] described the occurrence of four small calcified tuberculomas in a 7-year-old child. The presence of eleven calcified tuberculomas, as observed in Case 1, appears quite unusual in this respect. To my knowledge there is no other proved case in the literature in which such a great number of lesions was detected during life.

A brief consideration of the gross pathologic features of cerebral tuberculomas may explain the radiologic pattern of the individual lesions. The pathologic study of Evans and Courville[6] revealed that intracranial tuber-

culomas usually contain three distinct zones. The center consists of a structureless caseous core, whereas the outer zone is formed by partially or completely hyalinized connective tissue. At the junction of these layers calcification may take place, with formation of an intermediate calcareous zone surrounding the necrotic focus. This calcareous layer usually becomes indented and fractured as the outer zone of connective tissue shrinks and the necrotic center of the tuberculoma is absorbed or calcified.

On the basis of these pathologic findings, Weinberger and Grant[3] analyzed the literature and observed that the calcareous deposits in tuberculomas of the brain will frequently cast a characteristic shadow on roentgenographic examination. The individual calcifications are usually rather homogeneous in their center, but have a serrated, lacelike, angular margin, representing the intermediate calcified zone of the tuberculoma. In those lesions in which the indentation and fragmentation of the calcareous shell are more pronounced, small calcium spicules and plaques seem to be separated from the main center of calcification. The tuberculomas thus lose their originally compact structure, becoming irregular in outline and varying greatly in their various dimensions. These roentgenologic features are illustrated to advantage in a roentgenogram of the brain in Case 1 (Fig. 6). The calcareous lesions disseminated throughout the cerebrum and cerebellum are seen to have a distinctly serrated and angular profile. Several of the larger lesions disclose a very irregular contour, indicating considerable distortion and fragmentation of the calcareous shell.

DIFFERENTIAL DIAGNOSIS

Though the roentgenologic appearance of calcified intracranial tuberculomas is frequently very characteristic, collateral clinical evidence should always be sought in differential diagnosis from other calcified intracranial lesions. It is beyond the scope of this paper to describe in detail the various types of pathologic intracranial calcifications occurring in childhood and their differential diagnosis. In the following paragraphs, some of the more important calcifying intracranial lesions will be briefly discussed.

Among neoplastic conditions, craniopharyngiomas and angiomas deserve foremost consideration. In craniopharyngiomas, the calcification may be flocculent or linear, extending frequently into the pituitary fossa, which is usually enlarged and deformed.[10] Calcification in angiomas assumes a characteristic double contour and is cast into a tortuous and racemose pattern with predilection for the occipital areas of the brain.[11] Calcification of subdural hematomas usually consists of linear strands and plaques close to the inner table of the skull.[12] Gliomas in childhood rarely calcify as extensively as tuberculomas except for ependymomas, which would be difficult to differentiate on the basis of roentgenologic observations alone.[13]

In the presence of multiple calcified tuberculomas, several conditions enter the differential diagnosis. Of foremost importance are the cerebral calcifications observed in tuberous sclerosis. In this condition the calcified lesions are usually discrete, smooth in outline, and in close relationship to the ventricular system,[14] though cortical lesions have also been observed in this disease. The differential diagnosis is usually not difficult, if attention is paid to the cutaneous manifes-

tations of this disorder (adenoma sebaceum, cutaneous fibromas, and café au lait spots) and to the mental retardation exhibited by patients with this disease.

Recently, cerebral calcifications due to toxoplasmosis have attracted a great deal of attention.[12] In this protozoan infection, multiple flocculent calcifications usually not more than 2 mm. in diameter are found to be scattered throughout large areas of the brain. In addition, curvilinear calcifications entirely unlike those observed in tuberculoma have been described. The presence of chorioretinitis, hydrocephalus, or microcephalus is a common finding in this condition and is of considerable importance in differential diagnosis.

Among the rarer intracranial calcifications in childhood, symmetrical calcification of the basal ganglia should be mentioned.[15] The calcification in this condition is usually flocculent, though occasionally coalescence of these small densities may occur. The typical location and symmetrical distribution of these lesions, as well as clinical signs of hypoparathyroidism, are important in the establishment of a correct diagnosis. In so-called calcification epilepsy,[16] a large number of small, nodular, smooth calcifications may be disseminated throughout the cerebral cortex. The great number of the lesions, their smooth contour, and familial occurrence should be of aid in differential diagnosis.

CLINICAL CONSIDERATION

The clinical signs and symptoms of tuberculoma are difficult to evaluate in those cases in which tuberculous meningitis overshadows all other clinical features. Rich and McCordock[17] have emphasized that the development of tuberculous meningitis usually can be traced to the rupture of a cortical or meningeal tubercle into the subarachnoid space with subsequent discharge of organisms into the cerebrospinal fluid. Nevertheless, the formation of an intracranial tubercle does not necessarily lead to the immediate development of meningitis, nor will all tuberculomas ultimately take this course.

In those cases in which the intracranial tuberculoma remains isolated, the clinical symptomatology depends largely upon the site of the lesion. Tuberculomas of the cerebrum, because of their predilection for the cortex, are frequently the cause of generalized or jacksonian convulsions. Signs of increased intracranial pressure rarely develop in these cortical lesions since they are usually limited in size. On the contrary, tuberculomas of the cerebellum and brain stem not infrequently cause obstruction of the ventricular system or subarachnoid pathways. Generally, intracranial tuberculomas are difficult to differentiate from other space-occupying intracranial lesions, which is demonstrated by the frequency with which they are removed under the mistaken diagnosis of brain tumor.

Undoubtedly, there is a significant number of patients in whom tuberculomas of the brain may remain temporarily or permanently asymptomatic. This is well illustrated in Case 1 of this paper, in which no cerebral manifestations were apparent up to the time of the terminal illness. It is striking that this extensive disseminated tuberculous process of the brain remained clinically silent for a considerable period of time. This observation emphasizes that in the differential diagnosis of both symptomatic and asymptomatic cerebral calcifications, tuberculomas deserve proper consideration.

SUMMARY AND CONCLUSION

Tuberculomas of the brain are more frequently observed in childhood than in adult life. In a small number of cases calcification of the lesions has been observed.

On roentgenographic examination calcified tuberculomas of the brain have a characteristic serrated and angular appearance which should frequently permit their differentiation from other calcifying intracranial lesions. Calcifying tuberculomas may occur as solitary or multiple lesions in any portion of the brain, rarely measuring more than 3 cm. in diameter.

Three cases of calcified intracranial tuberculomas are presented. In two cases, the lesions were multiple and in one case, solitary. In the first case the roentgenologic observation of multiple calcified cerebral tuberculomas was confirmed on autopsy. In the other two cases the history of active tuberculosis and the characteristic x-ray appearance make the tuberculous nature of the observed intracranial calcifications very likely.

It is conceivable that clinically asymptomatic cerebral tuberculomas occur more frequently than statistics indicate and that these lesions may remain unrecognized in the absence of roentgenologic studies.

Calcified tuberculomas of the brain should always be considered in the differential diagnosis of solitary or multiple, symptomatic or asymptomatic, intracranial calcifications.

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THE TREATMENT OF PNEUMOCOCCAL MENINGITIS WITHOUT INTRATHECAL PENICILLIN

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THE ill effects associated with intrathecal forms of medication in the treatment of meningitis have recurred with each new form of therapy as it has developed. With the use of serum and each of the sulfonamides, the intrathecal route has been first advocated and then discarded. At present, intrathecal penicillin is still generally accepted in the treatment of pneumococcal meningitis, although there are some indications that it is losing favor. Rammelkamp and Keefer[7] and others[8, 9] have presented evidence that penicillin given by the intravenous or intramuscular route does not diffuse readily into the cerebrospinal fluid. In experimentally induced pneumococcal meningitis in dogs, systemic penicillin alone proved inferior to systemic and intrathecal administration.[10] However, it has been demonstrated that acute inflammation of the meninges does promote diffusion of the antibiotic into the spinal fluid.[11] Reports showing that the intrathecal administration was not without danger[2, 15, 16] have led us to make limited use of this form of therapy. Subsequently, a few reports of single cases of pneumococcal meningitis treated successfully with intravenous or intramuscular penicillin have appeared.[12-14] Furthermore, there is a lack of convincing evidence that the introduction of penicillin into the subarachnoid space increases the concentration of the antibiotic in the meningeal tissues. All layers of this tissue are richly supplied with blood vessels or lymphatics or both. Since the infection is one involving the meninges, it would seem logical that the purpose of treatment would be to maintain a high concentration of the therapeutic agent in the tissues and not in the exudate. This can best be effected by adequate blood levels.

It is the purpose of this communication to report seventeen patients with meningitis due to pneumococci treated without intraspinal penicillin, fourteen of whom recovered.

GENERAL OBSERVATIONS

The individuals treated in this series are listed in Table I. Table II shows the distribution of the patients according to the amount of penicillin given and the results of therapy in terms of the percentage of patients who recovered and who suffered complications. Also a group of five individuals who received additional intrathecal medication are included in Table II. The patients ranged in age from 6 weeks to 63 years. Six were below 2 years of age and five were between 2 and 14 years of age. With one exception, all were treated with com-

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bined sulfadiazine and penicillin therapy. Type-specific antipneumococcal serum was not used in any of the patients included in Table I, but it was administered to two of those receiving intrathecal penicillin.

TABLE I. SUMMARY OF SEVENTEEN PATIENTS TREATED WITHOUT INTRATHECAL PENICILLIN

CASE NO., INITIALS, AGE	DURATION OF ILLNESS PRIOR TO ADMISSION (DAYS)	CONDITION ON ADMISSION	SPINAL FLUID NO. CELLS, TYPE PNEUMOCOCCUS	DURATION OF FEVER IN DAYS IN HOSPITAL	OUTCOME
1. N. M. 52 yr.	1	Comatose T. 105° F.	4,000 I	11	Recovery
2. N. G. 25 yr.	2	Comatose T. 105° F.	25,000 VIII	12	Recovery
3. I. B. 4 mo.	3	Comatose T. 103° F.	15,000 XIX	37	Recovery Brain damage
4. R. B. 3 mo.	14	Lethargic T. 100° F.	624 VII	42	Recovery
5. G. L.* 6 mo.	10	Comatose T. 105° F.	240 I	124	Death in 124 days
6. F. M.* 14 yr.	30	Comatose T. 104° F.	17,300 IV	–	Death in 2 hours
7. E. S.* 8 yr.	14	Irrational T. 104° F.	8,000 III	–	Death in 18 hours
8. D. W. 7 yr.	5	Comatose T. 105° F.	1,600 III	8	Recovery
9. D. C.* 17 yr.	7	Irrational T. 104° F.	9,000 XXVIII	4	Recovery
10. M. L. 2 yr.	14	Comatose T. 104° F.	3,500 XVIII	4	Recovery
11. C. P. 4 yr.	2	Comatose T. 103° F.	2,000 ?	18	Recovery
12. I. S. 3 mo.	1	Moderately ill T. 104° F.	600 IV	17	Recovery
13. E. R. 40 yr.	1	Comatose T. 102° F.	8,000 ?	10	Recovery
14. F. S.* 63 yr.	40	Comatose T. 101° F.	3,000 ?	8	Recovery
15. T. D.* 16 yr.	25	Comatose T. 103° F.	2,600 I	4	Recovery
16. A. G. 4 mo.	5	Comatose T. 105° F.	1,200 VII	22	Recovery Brain damage
17. S. B. 6 wk.	1	Lethargic T. 103° F.	1,000 VII	10	Recovery

*Signifies therapy with sulfonamides and/or penicillin before admission to this hospital.

TABLE II. A COMPARISON OF RESULTS OF COMBINED SULFADIAZINE AND PENICILLIN THERAPY IN PNEUMOCOCCAL MENINGITIS*

GROUP	NO. PATIENTS	AVERAGE DAILY DOSE PENICILLIN (UNITS)	PER CENT RECOVERED	PER CENT COMPLICATIONS
A	10	120,000-160,000	70	10
B	7	320,000-400,000	100	14
A and B (Total of all patients treated with systemic penicillin)	17	120,000-400,000	82	12
C (Patients treated with systemic and intrathecal penicillin)	5	120,100-160,000 I.M. or I.V. 5,000-20,000 intrathecal	80	60

*All but one of the patients received sulfadiazine.

The duration of illness in all patients prior to admission, including those with intrathecal therapy, varied considerably (Table I). Only two patients were referred to this hospital with an established diagnosis of meningitis confirmed by a lumbar puncture before admission. Ten of the patients had evidence of an otitis media for days or weeks before admission, and four had findings of pneumonia at the time they were admitted. Three patients also were proved to have mastoiditis. Only four showed no evidence of a complicating infection at the time they were first seen here or gave no history of such an infection. The time of onset of meningitis in most of these patients is obviously difficult to estimate. This is particularly true in the infants and children. With the exception of one patient, it is probable that meningitis was present in most for only a brief period before the time of admission to this hospital. Fourteen of the patients had received no specific therapy before being seen here. The remaining eight had either sulfonamides, penicillin, or both for varying intervals of time before admission.

BACTERIOLOGIC STUDIES

Bacteriologic diagnosis was made by smear and culture of the spinal fluid. Cultures were positive in all except one patient, who had positive cultures in another hospital and had organisms seen in the spinal fluid smears on two occasions after admission here. One patient had a positive culture but a negative spinal fluid smear. Pneumococcal typing was done on all but three patients. In most of the patients lumbar punctures were done on admission and again forty-eight hours later, or more frequently as seemed indicated by observation of the individual case. Particular emphasis was placed on the persistence of a positive culture or smear. Routine cell counts, sugar, and protein determinations of the spinal fluid were also made at these times. Blood cultures were taken at the time of admission on five patients, and all were negative.

RESULTS

Fourteen of the seventeen patients treated with systemic penicillin and sulfadiazine recovered from the meningitis, a rate of 82.3 per cent, which compares very favorably with other series reported in the literature.[1-6] These findings are listed in Table II. Three patients died while on this form of therapy, two within eighteen hours of the time that they were first seen at this hospital. The third patient lived 124 days and at autopsy showed no evidence of active infection. However, there was marked cortical atrophy and degeneration plus internal hydrocephalus. Two of the fourteen patients who recovered had severe mental retardation.

Not one of the patients who responded to therapy had a relapse of the meningitis. To minimize this common occurrence, dosage should be adequate and continued long enough to eradicate completely the quiescent foci of infection. The average duration of therapy in patients who recovered was twelve days after the temperature returned to normal.

A further analysis of the data indicates that regardless of the antecedent type of pneumococcal infection (i.e., otitis media, pneumonia, etc.) the results

of therapy were favorable. Moreover, as shown in Table I, the duration of such illness previous to therapy did not seem to influence the final outcome. Eighty-two per cent of the patients showed some foci of infection other than meningitis. It is interesting to note that the factor of age had little significance prognostically. Deaths were rather evenly distributed over the entire age span, and complete recovery occurred in both the youngest and the oldest patient. However, all patients who had sequelae of brain damage were less than a year of age. The type of pneumococcus did not influence the course of the disease. A similar observation regarding the pneumococcus type has been reported by White and his associates[6] in a series of fifty patients. No significant prognostic value could be attached to either the sugar or protein content of the spinal fluid with repeated determinations during the course of each illness.

The severity of illness was no greater in the five patients who received the intrathecal penicillin than in the others. Unfortunately, results in this group are not significant because of the small number. There was one death, and three patients had neurological complications. One of the sequelae, a seventh and eighth nerve paralysis, may have been due to the accompanying mastoiditis and mastoidectomy. Nevertheless, the high incidence of complications in this small group plus others reported in the literature associated with intrathecal penicillin[2, 15, 16] should make one cognizant of the potential danger of this form of therapy. Although it is recognized that no definite proof is given in this series, the impression of a poor effect is obtained.

DISCUSSION

The fact that treatment of pneumococcal meningitis systemically resulted in a recovery rate as good as in reported series where intrathecal therapy was used indicates that the latter, in most instances, is unnecessary. Moreover, as previously mentioned, some ill effects have been observed with intraspinal penicillin. It should be stressed that each patient should be treated individually. Careful observation during the first twenty-four to forty-eight hours of illness with repeated lumbar punctures and bacteriologic examination of the fluids should be an accessory guide to therapy.

No precise statement can be made concerning the dosage of sulfadiazine or penicillin. It should be emphasized that the sulfonamide is as important as the penicillin in the therapeutic program. The average amount of sulfadiazine given to infants and children in the present study was 0.2 Gm. per kilogram of body weight (1.5 gr. per pound) per twenty-four hours. In adults the average doses were 6.0 to 8.0 Gm. per day. No untoward results were encountered though most of the patients were kept on this medication for periods longer than two weeks. The average daily doses of penicillin in Group A, Table II, were 120,000 to 160,000 units intramuscularly. A few patients also received 10,000 to 30,000 units intravenously at the start of therapy. In Group C intrathecal penicillin was given, in addition to the systemic injections, in dosages of 10,000 to 15,000 units once or twice a day for an average of four days. In Group B, the dosage of penicillin averaged from 320,000 to 400,000 units intramuscularly daily, and in addition several patients received an initial

100,000 to 200,000 units intravenously. No intrathecal penicillin was used during this latter period (from 1946 to the present), and all seven of the patients recovered (Cases 11-17, Table I). The amounts just specified were used regardless of age and were given at three-hour intervals. In Group A the average duration of therapy was thirty days, and in Group B the average duration of therapy was twenty-two days. In both groups sulfadiazine, as well as penicillin, was given for the entire time in the majority of instances (Table II). Although the number of cases is small, it would seem that the use of larger doses of the antibiotic gave better results than in the earlier cases where smaller amounts were used. Another possible factor contributing to differences in these results may have been the changes in the production of penicillin resulting in a more uniform product, which was administered to the individuals in Group B.

In only one case can it be stated that adjunctive use of intrathecal penicillin may have accomplished more than systemic penicillin alone. This was in the only patient who had persistently positive spinal fluid cultures (for ten consecutive days) until intrathecal penicillin was given. Other factors may have influenced the elimination of the organism from the spinal fluid. Concurrent with the introduction of penicillin into the subarachnoid space, the dose of intramuscular penicillin was increased and antipneumococcal serum was administered. In addition, it was noted on several previous examinations at this hospital that the patient was mentally retarded. Transillumination of the head showed a marked defect of intracranial structures in the frontal regions. What effect, if any, the intracranial anomaly had upon the course of the disease is difficult or impossible to evaluate. All other patients had negative spinal fluid cultures and smears of the fluid sediments within forty-eight hours of the time that specific therapy was instituted. In one patient treated without intrathecal penicillin, in whom more frequent lumbar punctures were done, the spinal fluid culture became negative in six hours.

SUMMARY

The treatment of seventeen patients with pneumococcal meningitis with sulfadiazine and penicillin resulted in a recovery rate of 82 per cent. No intrathecal penicillin was used in this group. Seven were treated with relatively large doses of penicillin (320,000 to 400,000 units daily) with a recovery rate of 100 per cent.

The therapy of pneumococcal meningitis should be individualized for each patient, and intrathecal penicillin should be reserved for those who do not respond to adequate systemic therapy.

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Addendum

Since the preparation of this manuscript we have treated one other patient with pneumococcal meningitis as outlined above without intrathecal penicillin. She was an infant 10 months of age and recovery was apparently complete.

MORTALITY OF ACUTE INFANTILE DIARRHEA AT THE LOUISVILLE GENERAL HOSPITAL FROM 1943 TO 1947

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IN 1944 Glaser and Bruce[1] reported 180 cases of diarrhea seen at the Louisville General Hospital during the months of July, August, and September from 1940 to 1942. There were thirty-two deaths, or a mortality rate of 17.8 per cent. In 1942 they had fifty-eight cases during these three months with six deaths, or a death rate of 10.3 per cent. The reduction in the mortality rate was believed to be due to certain changes in therapy. Since 1942 we have admitted 570 infants with acute diarrhea to the Louisville General Hospital. Sixty-two of these patients died. The death rate was 10.9 per cent. Although the plan of treatment has changed very little, there has been a marked variation in the fatality rate from one month to the next, and from one year to another. For example, in 1943, during the month of October, there was an 8 per cent mortality, while in November of the same year, there were no deaths. In 1943 the death rate was 13.9 per cent, and in 1944 it was only 4.6 per cent. Because of the different severity of diarrhea during certain months or years, it is very difficult to evaluate properly any plan of therapy unless a control group is available at the same time the new treatment is being used.

In 1943 the majority of the infants were treated as described in the report of Glaser and Bruce. This consisted of starvation for twelve hours in moderately severe cases and for as long as thirty-six hours in the very severe cases. During this period, sips of boiled water were sometimes given. A continuous intravenous drip was begun at the onset of treatment. One-sixth molar sodium lactate was usually given immediately, followed by 5 per cent glucose in saline. Not more than half of the total daily fluid contained saline. At least three ounces of fluid per pound of body weight were given intravenously each day of the starvation period. On the second day of treatment, plasma or blood was often given. Whenever possible, a needle was inserted into a vein without "cutting down," but in most instances of severe diarrhea, it was necessary to cannulate the vein.

If the patient improved after twelve to thirty-six hours, he was offered buttermilk every three or four hours, and was allowed to take as much of this milk as desired. In those patients who refused buttermilk, boiled skimmed milk was given. When the diarrhea ceased, the feeding was gradually changed to a whole milk or an evaporated milk formula.

Nearly all infants received either sulfathiazole or sulfadiazine in a daily dosage of one grain to one and one-half grains per pound of body weight. This

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was usually administered subcutaneously in a 5 per cent solution during the period of starvation, after which the medication was given by mouth. A few patients received sulfaguanidine.

In 1944 treatment remained much the same as previously described, except that the infants were started on a small amount of buttermilk and this gradually increased.

During 1945 and 1946 longer periods of starvation were employed, and in severe cases, intravenous fluid was given for forty-eight or seventy-two hours. In patients with recurrence of diarrhea, starvation was repeated. Greater attention was also given to the administration of plasma to provide needed protein. Except for a few patients who received lactate Ringer's solution, no fluid containing potassium[2] was given.

Buttermilk, boiled skimmed milk, or Protein milk was used in small amounts after the period of starvation. The milk was gradually increased, and before discharge, the patient usually was on an evaporated milk or a whole milk formula.

The intern and resident staff performed all treatments. Only patients who had not responded to outpatient care or those who were dehydrated when first seen were admitted to the ward. No newborn infants were included in this report, except eight premature infants who were admitted in 1946. The chief complaint in all cases was diarrhea, but about 5 per cent of the patients had some other evidence of infection. Bronchopneumonia and otitis media were most common.

TABLE I. MORTALITY RATE IN ACUTE DIARRHEA 1943 THROUGH 1946

YEAR	NO. CASES	NO. DEATHS	MORTALITY RATE (%)	CORRECTED MORTALITY RATE (%)
1943	201	28	13.9	11.2
1944	87	4	4.6	4.6
1945	136	14	10.3	8.3
1946	146	16	11.0	3.7
Total	570	62	10.9	7.5

The mortality rates are shown in Table I. The highest death rate, 13.9 per cent, occurred in 1943, although the treatment was the same as that given in 1942. During July, August, and September, 16.2 per cent died in 1943, while the fatality rate was 19.3 per cent during the same months in 1942. The lowest fatality rate was found in 1944 when only 4.6 per cent died. During July, August, and September of that year the death rate was 10.2 per cent. Fewer cases occurred during that year, and since only minor changes in therapy were instituted, it seems justifiable to conclude that the disease was of less severity than usually encountered.

The "corrected mortality" given in Table I was calculated with omission of those patients who died within the first twelve hours. In 1946 there were four patients who died within two hours after admission, giving a corrected mortality rate of 9.1 per cent. During 1946 eight premature infants were transferred from a premature station in which an epidemic of diarrhea was present. The mortality rate had been over 90 per cent at this premature nursery, and we were able to save only one of the eight. Because of the recognized high

mortality rate of epidemic diarrhea in premature infants, the "corrected mortality" of 3.7 per cent was calculated by omitting these eight infants.

During this four-year period, there were 447 white infants with forty-seven deaths, giving a mortality rate of 10.5 per cent. There were 123 Negro infants with fifteen deaths, or a death rate of 12.2 per cent.

The mortality rate according to age is shown in Table II. In general, the younger the infants, the higher the death rate. Fifty per cent of the infants who died were under 4 months of age. Likewise, the smaller the infants at time of admission, the higher the fatality rate. Forty-eight per cent of the infants who died weighed less than 8 pounds. There was a definite seasonal incidence encountered, and 64 per cent of the cases occurred during the months of July, August, September, and October. The mortality rates during July and August were no higher than the average, but in September and October the fatality rate was 15.4 per cent and 14.3 per cent respectively, as compared to the average rate of 10.9 per cent.

TABLE II. MORTALITY RATE ACCORDING TO AGE

AGE (MONTHS)	NO. CASES	NO. DEATHS	MORTALITY RATE
0-3	190	31	16.3%
4-6	126	15	11.9%
7-12	118	7	5.9%
13-up	136	9	6.6%

The milk that the infant was receiving at the time of the onset of diarrhea seemed to influence the prognosis. Although a good number of the infants were nursing the breast at the time of admission to the hospital, none of these infants died. There was not a single death in four years of an infant who developed diarrhea while nursing the breast.

At least three stool cultures were obtained from all patients except those who died shortly after admission. Among the 570 cases there were only three patients from whom the cultures were positive for dysentery organisms, and these belonged to the Flexner group. *Bacillus typhosus* was isolated from the stools of two infants admitted because of severe diarrhea. Both patients with typhoid recovered, but one patient with dysentery died. Despite the use of rectal swabs and efforts to inoculate the culture plates immediately, the number of positive stool cultures remained surprisingly small.

Weihl and his associates[3] have recently reported on the mortality rate of infants with acute diarrhea seen at the Cincinnati General Hospital during the years 1944 and 1945. There were 292 patients with a total of twenty-two deaths. The combined fatality rate for the two-year period was 7.5 per cent. The corrected mortality rate was 5.6 per cent. Because of the similar climate and sectional location of Louisville, it was of interest to compare these mortality rates with those obtained here during the same period. In our series there were 233 cases with 18 deaths in 1944 and 1945. The mortality rate was 8.1 per cent, and the corrected mortality rate was 5.8 per cent.

SUMMARY

The mortality rate of acute diarrhea of infants varies greatly during different months or years.

From 1943 through 1946, 570 patients with severe acute infantile diarrhea were admitted to the Louisville General Hospital. Sixty-two of the patients died. The death rate was 10.92 per cent, and the corrected mortality rate was 7.5 per cent.

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Case Reports

IDIOPATHIC HYPOPARATHYROIDISM

A Case Simulating Epilepsy and Brain Tumor

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IDIOPATHIC hypoparathyroidism is a known clinical entity.[4] The criteria for diagnosis are: (*A*) low serum calcium level; (*B*) high serum inorganic phosphorus level; (*C*) normal skeleton as demonstrated by roentgenography; (*D*) absence of all signs of renal insufficiency. In many patients, the cause of hypoparathyroidism is obvious, such as inadvertent extirpation of the parathyroid glands following thyroidectomy. In other patients, the cause of the hypoparathyroidism is often very obscure. In these cases, the term "idiopathic" hypoparathyroidism is used. Reports on the pathologic changes of this entity are meager. Yanase[5] reported hemorrhages in the parathyroids of infants, presumably secondary to birth trauma or neonatal asphyxia. Such injuries often resulted in the hypoplastic glands which were found later in life. The hemorrhages ranged from slight extravasations of blood to massive infiltrations; some of the patients manifested tetany, others did not. Drake[1] reported a case in which the parathyroids were completely replaced by fatty tissue. He also referred to acute infections as the possible etiological agents[6] of the degeneration of parathyroid tissues. It is interesting to speculate upon the role of the severe infection in relation to the subsequent development of parathyroid disease. Acute infection was responsible for the first hospital admission of our patient; however, no specific predominating pathogen was demonstrated upon that admission. Drake[1] found no particular sex incidence in hypoparathyroidism, but noted that most patients reported fall into two age groups, childhood and middle life, very few cases being seen in adolescence or early adulthood.

Another factor which must be considered is that in some cases the symptoms, signs, and laboratory findings of hypoparathyroidism occur because of the lack of secretion of the parathyroid hormone, while in other cases, the patient may be able to produce parathyroid hormone, but the peripheral tissues of the body are unable to respond to this secretion. In such patients the symptoms, signs, and laboratory findings are identical with those found in patients in whom there is lack of production of the hormone. To differentiate the "true" idiopathic hypoparathyroidism—i.e., the condition in which no hormone is produced—from the "pseudo" hypoparathyroidism—i.e., the entity in which the peripheral tissues do not respond to the stimulus of the hormone—the Ellsworth-Howard test is used.[4] In this determination, parathyroid extract is injected intravenously and the response noted. The primary response is an increased urinary excretion of inorganic phosphorus associated with a lowering of the blood serum inorganic phosphorus and a rise in the blood serum calcium level. If the patient responds to the test by an increased urinary excretion of inorganic phosphorus, then the peripheral tissues are sensitive to the stimulus of the hormone and the disease is due to a deficiency in the elaboration of the hormone rather than to the inability of the body tissues to respond when it is present.

From the service of Dr. Harry S. Altman, pediatrician-in-chief, Lincoln Hospital.

The fact that true idiopathic hypoparathyroidism may simulate epilepsy or even brain tumor is not generally realized. Many of the standard works on neurology do not mention hypoparathyroidism in the differential diagnosis of epilepsy. Shelling,[2] however, in his book on the parathyroid gland stresses that (1) tetany of parathyroid origin must be differentiated from tetany due to other causes; and (2) tetany must be distinguished from epilepsy. The clinical signs in both syndromes are so very similar that even the most careful observer may readily mistake tetany for epilepsy and vice versa unless analysis of the serum calcium and phosphorus levels is made. Sutphin, Albright, and McCune[3] state that there have been three cases at the Massachusetts General Hospital which were diagnosed as idiopathic epilepsy and the patients followed for a period of years before the diagnosis of hypoparathyroidism was finally made by blood chemistry. In the same article, they report a patient with idiopathic hypoparathyroidism who was admitted to the hospital with signs of increased intracranial pressure, choked discs, and convulsive seizures. A cerebral neoplasm was suspected, but electroencephalograms and ventriculograms were normal. Following adequate therapy for the hypoparathyroidism, the papilledema disappeared. This increase in intracranial pressure occurring in hypoparathyroidism may readily simulate brain tumor or other expanding intracranial lesions and may easily mislead the clinician unless a serum calcium determination is made. The physiopathologic mechanism of the increase in intracranial pressure and papilledema is at present obscure. The importance of being aware of the similarity of cerebral neoplasm, epilepsy, and hypoparathyroidism has been mentioned by Levy,[7] who states: "This patient was in the paradoxical position of knowing what was producing her seizures, but because her symptoms did not fit in with the usual picture of tetany, she was labeled hysterical or epileptic."

The following case of idiopathic hypoparathyroidism is being reported because of its simulation, at various times, of both epilepsy and cerebral neoplasm.

CASE REPORT

E. R. was born of Puerto Rican parentage at the Lincoln Hospital on March 8, 1940. His mother was serologically negative, and delivery was spontaneous and normal. His neonatal period, growth, and development were apparently normal. The family history was noncontributory.

His first Lincoln Hospital admission was on Oct. 6, 1941 for severe acute tonsillitis, sinusitis, and erythema multiforme. A suggestive rachitic rosary noted on physical examination was not confirmed by x-ray studies. An electrocardiogram was normal. (See Table I, *a* for blood chemistry.) He was discharged Dec. 14, 1941.

The second admission was on Feb. 17, 1945, at the age of 5 years. Due to poor economic conditions at home the child had been placed in a children's shelter. Three days before release from this institution, he developed a fever, and the night before admission he complained of pain in the right calf, and a lump was noted in that area. He then developed pain in both hands, which was followed by spastic contracture of both hands and wrists. Physical examination on admission revealed a typical carpopedal spasm and positive Chvostek and Trousseau signs. Both of these signs were immediately relieved by administration of 10 c.c. of calcium gluconate intravenously. Laboratory studies revealed a normal blood cell picture and hemoglobin, normal urine, and negative serology. No pathologic change was seen in x-rays of the chest and long bones. The Mantoux test was negative. The chemical study of the blood is shown in Table I, *b*. The child was given calcium gluconate and water-soluble vitamin D preparation orally. He became a diphtheria carrier and was transferred to a contagion hospital.

TABLE I. BLOOD CHEMISTRY DETERMINATIONS

DATE	CALCIUM (MG. %)	INORGANIC PHOSPHATE (MG. %)	ALKALINE PHOSPHATASE (BODANSKY UNITS)	TOTAL PROTEIN (GM. %)	ALBUMIN (GM. %)	GLOBULIN (GM. %)	UREA NITROGEN (MG. %)	CO_2 COMBINING POWER (VOL. %)	CHOLESTEROL (MG. %)	CEPHALIN FLOCCULATION
First admission										
a. Oct. 20, 1941	10.4		7.0	5.3	3.6	1.7	12.0			
Second admission										
b. Feb. 18, 1945	6.6	7.8	8.1	7.2	4.7	2.5	13.0	48		
Interval during which no vitamin D was given										
Third admission										
c. Oct. 23, 1945	6.8	7.1	13.2	7.4	4.1	3.3	14.5		205.0	Neg.
5,000 units of vitamin D and 1.5 Gm. calcium chloride given daily										
d. Dec. 5, 1945	7.2	5.7	4.8						178.0	Neg.
e. Dec. 13, 1945	12.2	6.0	6.1							
f. Dec. 26, 1945	11.5	4.5	3.2							
Calcium chloride omitted										
g. Jan. 7, 1946	10.2	3.0	11.2							Neg.
Medication not taken regularly										
Fourth admission										
h. April 22, 1946		11.1	3.4							
i. April 26, 1946	7.8									
j. May 10, 1946	7.0			7.4			14.7		247.0	
k. Sept. 12, 1946	9.3	3.9								
l. Oct. 28, 1946	7.4									
Stabilization on oral calcium gluconate, vitamin D, and dihydrotachysterol										
Fifth admission										
m. March 15, 1948	8.6	4.5	6.0	7.0	4.4	2.6	16.0		182.0	Neg.

Glucose Tolerance Test (mg. %)

DATE	FASTING	½ HR.	1 HR.	2 HR.	3 HR.	4 HR.
Oct. 15, 1945	73	84	91	71	66	66

He was seen for the third time eight months later on Sept. 21, 1945. Thrice during the preceding week the child had had episodes of syncope and unconsciousness, each of about ten minutes' duration, which occurred while he was playing in the street. There were no associated convulsions. No vitamin D preparations had been given during this eight-month interval. Physical examination on admission was essentially normal. There was no sensitivity manifested to carotid sinus pressure. Laboratory studies showed normal blood count, serology, urinalysis, electrocardiogram, and x-rays of skull, chest, and long bones. The blood chemistry determination is shown in Table I, *c*. Results of the Ellsworth-Howard test are shown in Table II. This test confirmed the diagnosis of true idiopathic hypoparathyroidism. The ophthalmologist found no retinal abnormalities or cataracts. A glucose tolerance test was done on Oct. 15, 1945 (see foot of Table I).

While in the hospital, the patient was observed by a number of investigators to have "seizures," which occurred as many as six times in one day. These episodes occurred while the child was sitting at rest or playing in bed, and on several occasions they seemed to be directly precipitated by the overbreathing associated with emotional excitement. The patient would suddenly be seized with a clonic contraction of the right upper and lower extremities and a twitching of the entire right side of the face; a few seconds later he would show slight cyanosis of the lips; and then after a lapse of from thirty to sixty seconds the

attack would terminate, and he would sink to the bed exhausted. There was a considerable degree of clouding of consciousness during an attack, but the child could apparently hear questions that were put to him during the seizure and would answer them at its termination. He felt "sleepy" after an attack, but there were no residual neurological signs or other symptoms. A consultant endocrinologist believed these episodes to be attacks of petit mal epilepsy complicating an underlying idiopathic hypoparathyroidism. An electroencephalogram was done, the patient's cooperation being exemplary; this revealed an electrical pattern normal for the child's age.

Accordingly, it was postulated that the epileptiform manifestations were a sequel of the underlying endocrine dysfunction, and a therapeutic trial of the oral administration of 50,000 units of vitamin D and 1.5 Gm. of calcium chloride daily was begun on Nov. 28, 1945. On Dec. 5, 1945, blood chemistry determinations were done. (See Table I, *d*.) On December 13, the values were as shown in Table I, *e*, on December 26, as shown in Table I, *f*. On December 29, the calcium chloride was omitted from the therapeutic regimen. On Jan. 7, 1946 the levels were as seen in Table I, *g*. After the onset of therapy on Nov. 28, 1945, the patient did not have a single epileptiform manifestation of any description, and appeared to be normal in all his activities. On Jan. 15, 1946, a program was begun to reduce the vitamin D dosage gradually to a minimum daily requirement sufficient to prevent any epileptiform episodes. However, the child failed to appear at the follow-up clinic.

The patient again came under medical observation on April 22, 1946. He was admitted to another hospital because while at home he developed carpopedal spasm and laryngeal stridor. These signs were seen on admission, and twitchings of the face and rigidity of the muscles of the neck and abdominal wall were also present. A purulent drainage from a perforated right ear drum was noted. The child appeared acutely ill and was in a moderate state of anxiety. Medication had not been taken regularly during the interval between hospitalizations.

Laboratory work-up on admission revealed a mild polymorphonuclear leucocytosis and a normal urine. Serologic and tuberculin tests were negative. Serum calcium determination was not done on admission, but the other chemistry determinations performed during this fourth hospitalization are shown in Table I, *h*, *i*, *j*, *k*, and *l*. The basal metabolic rate was plus 4. Electrocardiograms taken before and after intravenous injection of calcium gluconate were normal. X-rays of the skull and long bones showed no abnormalities. An electroencephalogram taken fifteen days after admission showed an electrical dis-

TABLE II. ELLSWORTH-HOWARD TEST

DATE	TIME	VOLUME OF URINE EXCRETED (C.C.)	TOTAL INORGANIC PHOSPHORUS CONTENT (MG.)	SERUM CALCIUM (MG. %)	SERUM INORGANIC PHOSPHORUS (MG. %)
Oct. 28, 1945	9-10 A.M.	26	23.4	7.0	7.1
	10 A.M.—*2 c.c. of parathyroid extract intravenously*				
	10-11 A.M.	34	51.0	--	--
	11-12 N	39	90.0	--	--
	12 N-1 P.M.	15	34.0	8.0	6.0
June 10, 1946	7 A.M.	50	35.5		
	8 A.M.	20	11.4		
	10:05 A.M.	150	33.3		
	10:15 A.M.—*2 c.c. of parathyroid extract intravenously*				
	10:20 A.M.	200	--		
	11:20 A.M.	12	136.0		
	1:20 P.M.	4	26.0		
	2:15 P.M.	85	15.6		

charge rate slightly slower than that of the average subject of the patient's age. A Stanford-Binet test, despite language difficulties, showed an intelligence quotient of 92. Dental x-rays showed malocclusion of the teeth but otherwise were unremarkable. No nail changes were noted at this time.

On May 1, 1946, examination of the optic fundi was not remarkable, but on May 15, 1946, the optic discs were noted to be elevated and the retinal vessels tortuous. These findings remained the same for the duration of hospitalization. A lumbar puncture performed on May 21, 1946, with the child struggling moderately, showed a pressure of 210 mm. of water, the fluid being otherwise normal. A visual field examination was done on May 30, 1946, and a constriction of from five to ten degrees in all meridians was found. An Ellsworth-Howard test was done on June 10, 1946 (Table II); again the diagnosis of idiopathic hypoparathyroidism was confirmed. The neurological staff consultants felt that to rule out a cerebral neoplasm a ventriculogram was indicated, which was done on Sept. 27, 1946, after the patient had had normal serum calcium levels for a period of over two months with no changes seen in the degree of papilledema. The ventriculograms were normal. Another lumbar puncture was done following ventriculography with the aid of 0.2 Gm. of nembutal, and the pressure was 150 mm. of water. On admission the child's tetany had been treated with 10 c.c. of calcium gluconate intravenously, and then he was placed on oral calcium and vitamin D preparations for the rest of his hospital stay. He was finally stabilized on a regimen of oral calcium gluconate, vitamin D, and dihydrotachysterol; this served to maintain his serum calcium at levels above 9.0 mg. per cent. The purulent otitis media had cleared while the patient was in the hospital, and he was discharged on Nov. 18, 1946. The final diagnosis was true idiopathic hypoparathyroidism and bilateral papilledema.

Fig. 1.—Showing advanced degree of koilonychia.

The patient again came under our observation on March 8, 1948. Since his hospitalization in November, 1946, he had been receiving daily doses of oral calcium gluconate, vitamin D, and dihydrotachysterol. He had been apparently normal in all respects, had had no seizures of any description whatsoever, and

was an honor student in his class at school. However, during the past six months he had begun to develop changes in his fingernails. Physical examination on this last visit revealed an advanced degree of koilonychia or "spooning" of the fingernails; the left great toenail was also affected. (See Fig. 1.) Koilonychia is one of the trophic disturbances of the ectoderm that may occur in chronic hypoparathyroidism. However, we were not able to demonstrate the presence of monilia organisms here, in contrast to the cases reported by Sutphin and his associates.[3] The skin of the body was normal in all respects. The optic fundi were normal. The teeth were also normal. The patient was now 8 years old, weighed 50 pounds, and was 45½ inches tall. The blood count was normal. Urine and serology were normal. The blood chemistry is shown in Table I, *m*. X-rays of the skull, chest, and long bones revealed no abnormalities. An electroencephalogram was entirely normal for the patient's age.

DISCUSSION

This case clearly illustrates the difficulty in distinguishing epilepsy and brain tumor from hypoparathyroidism. The only way by which the diagnosis of hypoparathyroidism can be made is by determination of the serum calcium and phosphorus levels. In view of the differences in therapy for the three conditions, it is essential that a correct diagnosis be made. We are of the opinion that before any person is labeled as an epileptic or operated upon for a brain tumor, a serum calcium and phosphorus determination should be performed. It is only by this simple procedure that hypoparathyroidism can be diagnosed, particularly in childhood.

SUMMARY

1. The literature has been reviewed with emphasis on the clinical aspects that may at times be common to the conditions of epilepsy, brain tumor (or other expanding intracranial lesions), and hypoparathyroidism. The last-mentioned state may be readily differentiated by serum inorganic phosphorus and calcium determinations.

2. A case of idiopathic hypoparathyroidism is reported which illustrates the resemblance among these three conditions.

We are indebted to Miss Fanya Woll for her cooperation in the blood chemistry studies.

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CONGENITAL FOLLICULOPUSTULAR ERUPTION

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INTRODUCTION

CONGENITAL pustular eruption appears to be a very rare condition, and its relation to congenital impetigo (congenital pemphigus neonatorum) is a controversial subject. It therefore seems justifiable to report the following case where a widespread folliculopustular eruption occurred in an infant delivered by cesarean section and where staphylococci were found on direct examination and by culture.

CASE REPORT

On Oct. 6, 1947, Mrs. F. K., age 33, was admitted to the hospital for an elective cesarean section. She was not in labor, and her membranes were intact. Her expected date of delivery was October 30. She had had three previous cesarean sections because a pelvic deformity resulting from poliomyelitis in childhood prevented normal delivery. She had felt exceptionally well during her pregnancy except for a "head cold" two weeks before admission. She had no disease of the skin. Her serologic test for syphilis was negative. At the time of entry into the hospital, blood and urine studies were normal. Her temperature was normal. At 8:20 A.M. Oct. 7, 1947, she was delivered by cesarean section of a male infant weighing 6 pounds, 11 ounces. The surgeon handed the infant to an assistant who aspirated the mucus and tied the cord. Abnormalities were not looked for at that time and none was observed. The infant was wrapped in a blanket, put in a basket, and removed to the nursery. While cleaning the infant a pustular eruption was observed. At this time the baby was less than 40 minutes old.

Scattered folliculopustular lesions were noted on the pubis, perineum, buttocks, thighs, axilla, shoulders, neck, chin, and scalp. The lesions were largest on the lower portion of the trunk (Figs. 1 and 2). These pustules were 6 mm. in diameter, tense, dome-shaped, and pierced by a central hair. Their bright yellow color stood out in sharp contrast to the background of normal newborn erythema. The lesions elsewhere on the body were smaller, diminishing to pinhead-size or less. Rupture of the larger lesions produced a thick, heavy, creamy pus. Smears of this purulent material revealed many gram-positive cocci in clumps. Staphylococcus colonies were obtained on culture. These were almost nonchromogenic and on primary isolation were tentatively called type albus. They were coagulase-negative when first isolated, but on serial transfer on special media they eventually produced more pigment and became weakly coagulase-positive.

Because building alterations were in progress, the infant had to be "isolated" in a corner of the general nursery. After smears and cultures were obtained the lesions were opened and painted with one per cent aqueous solution of gentian violet. Penicillin therapy, 10,000 units five times a day, was started. With this treatment the lesions readily subsided without crusting. Penicillin was stopped after two days, and an antiseptic powder was the only therapy employed. However, on the sixth day a few more lesions appeared in the groin. At

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this time the baby was moved to another floor. Ten thousand units of penicillin were given once a day, and gentian violet was applied locally. By the eighth day there was an apparent increase in the number of pustules. Therefore, the dose of penicillin was increased to 10,000 units every three hours for the next three days. This finally produced a complete regression of all lesions.

Aside from the skin eruption, the infant's progress was normal. He took his formula well and otherwise appeared healthy and comfortable. At no time during his hospital stay did his temperature rise above normal. Routine urinalyses on four occasions were negative. He was discharged on the seventeenth day.

The mother's postoperative course was uneventful. Her temperature remained at normal levels, and she was discharged on the eleventh postoperative day.

As mentioned previously, the infant was allowed to remain in the general nursery. His bassinette was set aside in one corner. A sterile gown and antiseptic solutions for bathing the hands were provided for anyone who handled him. Within one week fourteen cases of a similar eruption appeared among the newborn infants. All lesions were of the folliculopustular type, but smaller than in the original case. There were no bullous or vesicular lesions. Only the first three cases of this epidemic were cultured. In all three, pure cultures of *Staphylococcus aureus* were obtained. These strains were all coagulase-positive.

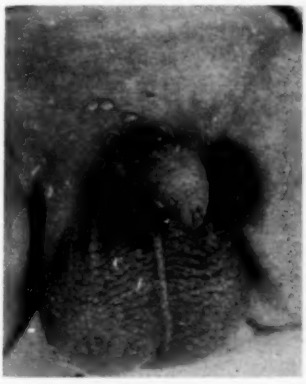

Fig. 1.

Fig. 2.

REVIEW OF THE LITERATURE

Congenital bullous impetigo is of rare occurrence. However, sporadic cases have been reported throughout the literature. This phase of the subject was first reviewed by Labardt and Wallart[1] in 1908 and later further reviewed and supplemented by Reed,[2] Freeman,[3] and others. An infant with congenital bullous impetigo delivered by cesarean section has been reported by Weston.[4] A review of the literature indicates that congenital exanthemas are next in order of rarity, and that a congenital pustular eruption is the most unusual of all. Certainly, reported cases of pure pustular eruptions, other than smallpox, occurring congenitally, are exceedingly few in number.

In 1928 Reed[2] reported a case of an infant born with a pustular eruption on the scrotum from which *Streptococcus hemolyticus* was cultured. The infant subsequently developed small pemphigoid blebs and a subdermal fluctuant mass on the scalp. All lesions subsided uneventfully. In 1931 Jordan[5] reported the case of an infant who showed many pustules at birth. On the sixth day of life an abscess developed in the left breast from which *Staph. aureus* was cultured.

The baby finally succumbed to an abscess of the scalp and a cellulitis of the neck on the seventeenth day. At wide variance with the conclusion of extreme rarity of this condition is Parmelee's[6] statment that he has observed six to eight cases of congenital pustules each year among the newborn infants at Cook County Hospital. Cultures taken in about ten instances were negative. In answer to an inquiry[7] Parmelee stated that the cases of which he spoke were similar in appearance to ours as shown in Figs. 1 and 2. Hence a revision of opinion may be in order. Apparently many cases of congenital pustular eruption have gone unreported in the past, and the condition, while still unusual, may not be as extremely rare as the paucity of available reports would indicate.

DISCUSSION

Most of the cases reported in the literature under the title "congenital pemphigus neonatorum" are of the bullous type. A few showed pustules and bullae mixed, while wholly pustular eruptions are the least common. These differences in the clinical picture long ago raised the question of classification. Reed[2] was of the opinion that his case of congenital pustular eruption represented a variant of congenital impetigo. He therefore proposed the name "pyodermatitis neonatorum" to encompass all pyogenic skin infections occurring congenitally or appearing in the newborn infant. Irgang and Alexander[8] later objected to Reed's comprehensive designation and defined as an entity a superficial pustular folliculitis which they observed in the newborn period. All their patients were normal at birth, the eruption first appearing during the early days of life. Cultures were done in only one instance, and *Staphylococcus albus* was obtained. The case reported herein is clinically similar to those described by Irgang and Alexander. Certainly the lesions in no way resembled those of a bullous impetigo, and it would be improper to designate the case as such. The bullous, pustular, and mixed varieties are in all probability alike in that each has its origin in an infectious agent. Their differences are probably due to variations in the strains of the causative organisms and their virulence, site of implantation, and other factors.

The question of the mode of transmission of the infectious agent from the mother to the fetus can only be speculated upon. Matzenauer,[9] Gilner and Nelson,[10] and others have postulated a transplacental route. Such an assumption infers a hematogenous infection in the mother. However, most of the mothers in reported cases were apparently well or had some trivial antecedent infection. Blood cultures, where done, were in most instances negative. If then a blood stream infection were present, it must certainly be mild and transient. That such a situation can exist is possible when it is remembered that not every organism introduced into the blood stream necessarily produces a septicemia. The quantity of bacteria introduced and the virulence chiefly determine the outcome. The circulating phagocytes and the fixed phagocytic cells (reticuloendothelial system) are continually aborting attempts at systemic infection. Yet it may be reasonable to assume that some organisms may escape such defense mechanisms in both mother and fetus and set up an infection in the latter. Still one other point needs explaining. Many of these infections appear so superficial that it seems probable that the infecting agent reached the fetal skin from without and not from within. This infers an infected amniotic fluid. Transfer of bacteria by direct passage through the fetal membranes, as, for example, from an infected cervix, may possibly occur. A transplacental spread to the fetus and thence to the amniotic fluid via the fetal urine is another surmised possibility.

The virulence of organisms causing congenital cutaneous infections (bullous, pustular, and mixed) apparently varies widely. In several instances the original superficial infection has become widespread or involved deeper tissues to pro-

duce death. The mortality percentage probably coincides with that given by Swendson and Lee[11] (20 to 50 per cent) for some past epidemics of pemphigus neonatorum before the advent of the sulfonamides and antibiotics. In other cases the process has been self-limited, and simple soap and water bathing has been the only treatment employed. Cultures of various organisms have been obtained. However, not all attempts at culture have been successful. Parmelee,[6] after his failure to culture organisms in congenital pustules, was inclined to believe that a nonbacterial irritant was at fault. Another explanation is that a self-sterilization process has overcome an infection of low virulence.

The role of an infectious agent in the case reported here is substantiated, but admittedly not proved, by the epidemic of clinically similar lesions following the introduction of the infant into the general nursery. It may be argued that the causal relationship is disproved by the difference in the strains of staphylococci isolated in the original and subsequent cases. However, this apparent discrepancy may be explained in two ways. A variety of staphylococci may have been present in the original case. Baerthlein,[12] as quoted by Reed,[2] was able to isolate four distinct types of staphylococci from a single bleb. On the other hand, the original staphylococci on repeated transfer on favorable media slowly became more chromogenic and coagulase-positive. Our bacteriologist (Dr. J. B. Miale) holds the opinion that the original strain of apparently weak pathogenicity was able to assume all the features of the typical pathogenic aureus variant when it grew on new and perhaps more favorable soil in the other three infants.

Freeman[3] suggested that unnoticed congenitally infected infants, placed in the general nursery, may be one source of origin of epidemics of impetigo neonatorum. The course of events in the present case tends to support such a theory.

The delay in discovering the eruption in the patient presented raises the question of whether the lesions were actually present at birth. Unfortunately, that question cannot be answered with finality. However, the clinical appearance of the lesions (size, various developmental stages, and thick, creamy contents) along with past experimental evidence makes it highly improbable that they developed within forty minutes. Dohi and Dohi,[13] in experimental inoculation of the human skin with staphylococci, produced erythema in several hours, but pinhead-sized vesicles were evident only after twelve hours. Epstein[14] inoculated human skin with both pure cultures of *Staph. aureus* and material from crusts of staphylococcic impetigo. Small blisters were produced in three and four days respectively.

SUMMARY

A case of congenital folliculopustular eruption occurring in an infant delivered by cesarean section is reported.

Clumped cocci were seen on direct smears taken from the lesions, and staphylococci were cultured.

An epidemic of clinically similar but less extensive cases developed following the introduction of this infant into the general nursery.

The literature on congenital pustular eruptions is reviewed.

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Medical Care

SURGICAL INDICATIONS IN GENITOURINARY TRACT INFECTIONS

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THE purpose of this paper is to offer our present concept of pediatric urologic problems, based upon twenty-five years of experience in the management of urologic problems of children in the St. Louis Children's Hospital. It is hoped that the material presented will be of assistance in the orientation of methods available for the study of urologic problems in children.

Restriction of the subject to infections of the genitourinary tract and their surgical approach necessarily limits the scope of the material which is covered, yet it should be noted that infection of some sort is associated with most urologic disturbances of children. Therefore, the prevention or elimination of infection is of frequent concern to both the pediatrician and the urologist in a great many urologic problems.

EXAMINATION

Urinalysis.—Urinary tract infections in infants and children which require urologic investigation and surgery constitute about one-tenth of those which are encountered. The remaining 90 per cent, predominantly pyelitis or pyelonephritis, respond to chemotherapy sufficiently well to render urologic study unnecessary unless repeated recurrences take place. An experienced observer can almost sense the child with an abnormality or defect in his genitourinary structures in which an associated infection has occurred, by the history of the illness and the child's appearance. Malnutrition and a history of long-standing or repeated urinary infections are the rule.

The investigation of a child suspected of having a surgical infection in the urinary tract begins with a careful microscopic examination of the urine. A clean, voided specimen of a boy will usually suffice for this purpose but a catheterized specimen is preferable in girls in order to avoid contamination from the external genitals. The urinary sediment should be fresh when examined. Microscopic study for cellular elements, i.e., white blood cells, red blood cells, and casts, as well as stains, either methylene blue or Gram, for bacteria, should be done because it may detect the presence of infection and give some indication of the nature of the infection as much as forty-eight hours before a culture report of the urine can be obtained. Pus and blood in the urine without demonstrable bacteria may cause suspicion of a tuberculous process and influence one to do acid-fast stains or guinea pig inoculations. An amicrobic pyuria, if a constant finding and substantiated by sterile cultures, may likewise suggest an entirely different type of chemotherapeutic approach.

Cultures of urines further define the nature of the infecting organism by identification, and this in turn permits a more selective form of chemotherapy. In isolated cases, further selectivity in drug therapy can be gained by the use of sensitivity tests, by determining effective concentrations for various drugs against the organism present.

Daily stains and/or cultures and frequent sensitivity tests may be essential in severe infections and their fluctuations from day to day may be of considerable importance in the management of the child's infection.

Further steps in the study of these children should proceed in a systematic, orderly fashion in order to minimize errors and omissions. This does not mean, of course, that one should pursue a routine course in a blind, unreasoning manner at the expense or sacrifice of sound clinical judgment. But it does implement such judgment and expedite the arrival at an accurate diagnosis if one follows a logical sequence of testing.

The presence or absence of residual urine must be determined early in these cases. The initial determination is the important one and great care should be taken to see to it that this is done accurately. Gentleness and a strict regard for asepsis should be exercised at all times. There is little risk if this is done. Prior instrumentation of any sort is likely to obscure the result, either by causing a retention by trauma where one did not exist before, or by aggravating a pre-existing one so that the accuracy of the observation is destroyed.

The type of catheter used will vary with the individual preferences of the physician. Our inclination is to use a small metal female catheter in girls, ranging from 10 Fr. to 16 Fr. according to age and size of the child, and an equally small semistiff coudé catheter in boys. These are usually more certain of introduction, even by one inexperienced in their use, and offer less chance of becoming contaminated during insertion than a soft rubber catheter. The important thing is to insert a catheter promptly after a voiding to get a true measurement of the amount of residual and to get the catheter into the bladder with a minimum of trauma.

Cystography.—Cystograms furnish a permanent record of bladder contour and capacity. The amount of fluid introduced into the bladder for this purpose will vary with the size and age of the child. Males normally have a smaller bladder capacity than females.

The picture of the bladder which is obtained with some intravenous urograms may eliminate the need for cystograms in some cases because the latter frequently outline bladder diverticula, distortions of the bladder, or foreign bodies quite well as the contrast media accumulates in the bladder. They do not, however, disclose regurgitation into the ureters in the dramatic way that a cystogram does. For this reason alone, cystograms are quite useful and can easily be made a part of the examination for residual urine if one is prepared to do the cystogram before the catheter is withdrawn.

The amount of fluid opaque media put into the bladder for a cystogram depends upon the patient's bladder capacity. The fluid should be allowed to flow into the bladder by gravity without undue pressure. If a residual is

present and the amount known, the same or nearly as much fluid may be introduced into the bladder. If no residual is present, an amount of opaque fluid comparable to that expelled in an average voiding can be used for the cystogram. A nonirritating fluid such as sodium bromide (7½ per cent solution) makes an acceptable medium for cystograms.

Fig. 1.—Cystogram. F. D., age 9; 600 c.c. residual urine; bilateral regurgitation of ureters with hydronephrosis and hydroureter.

Intravenous Urography.—There is much less hesitancy now in employing this useful agent for diagnostic purposes than formerly. Few ill effects have been noted from its use although ordinary precautions should be observed if the child is very ill. Furthermore, excretion of the drugs used for this purpose is usually poor in the face of severe renal insufficiency.

Too much should not be expected of intravenous urography in all cases. Where renal function is good and no obstruction or stagnation is present, the media may be excreted so rapidly that little notion of kidney architecture is obtained. The best that can be said in these cases is that kidney function is present. On other films, the radio-opaque material will be of insufficient concentration to show well, or perhaps be so obscured by intestinal gas as to have little if any pictorial value. Better films may be obtained on the first plate made and the films are of no value unless taken very shortly (within two or three minutes) after the agent is injected. The most serious disadvantage to intravenous urography is that the films frequently fail to show minor defects in the kidney, defects which may be shown in very good detail in retrograde

studies. Many intravenous urograms simply cannot be interpreted and provide nothing more than some idea of the degree of impairment in renal function.

They do provide a more physiologic and anatomic record than retrograde studies in some instances, particularly where stasis is present and where function, even if somewhat impaired, is still present to some degree. They are of great value if for any reason cystoscopy and retrograde pyelograms are not possible. On rare occasions, intravenous studies may serve to tell the story when retrograde studies have been unsatisfactory.

Fig. 2.—Intravenous urograms. D. W., age 13; kidney pelves well outlined and most of ureters visualized; kidney outlines distinct.

Retrograde Pyelography.—The improvements made in infant cystoscopes in recent years have greatly facilitated the urologic investigation of children. Vision has been improved even as the instruments have been made smaller and we can now view the bladder and urethra in very young infants. Nevertheless, it should be kept in mind that the structures in the genitourinary tract of a child are not as large as those of an adult. This fact, coupled with the miniature size of the cystoscopes, somewhat restricts the accuracy of the urologist's report and further limits his ability to do some things cystoscopically for children which are everyday practice in adults.

The superiority of cystoscopy and retrograde pyelograms over intravenous urography lies in the obvious advantage of (1) actually seeing within the bladder and urethra, (2) being able to catheterize the ureters to obtain separate urines from the two kidneys for microscopic study and culture, (3) securing

differential quantitative functional tests of the two sides, and (4) making repeated retrograde pyelograms, if necessary, until satisfactory films have been obtained.

All urographic studies of the kidneys, ureters, and bladder are better if intestinal gas is minimal. Children, particularly infants, show a great deal of this, perhaps because of their habit of swallowing air. We have discarded the routine use of enemas and usually rely on sedation alone for precystoscopic preparation. If fluoroscopy or a scout film before radiographic studies reveals too much gas for satisfactory films, the intravenous urography or cystoscopy with retrograde pyelograms may better be postponed until another time. Intestinal gas does not interfere so much with retrograde pyelograms as a rule because of the greater density of the radio-opaque media possible in the latter.

Fig. 3.

Fig. 4.

Fig. 3.—Retrograde pyeloureterograms. E. C., age 10; transurethral resection for bladder neck obstruction eight years previously.

Fig. 4.—Intravenous urograms. Unsatisfactory urograms on same patient as in Fig. 3.

Exploration and Biopsy.—There always remain certain individuals in whom these diagnostic procedures and the exercise of the best clinical judgment still leave the diagnosis in doubt. Frequently one has to fall back upon surgical exploration of a doubtful mass in the flank or upon inspection and biopsy of a questionable lesion.

SURGICAL PRINCIPLES AND METHODS FOR DIFFERENT INFECTIOUS CONDITIONS

The fundamental principle in the management of all surgical complications of infections in the genitourinary tract is the prompt establishment of free drainage and the elimination of all stasis. Every effort must be made to pre-

serve tissues and structures and to restore them to normal function. Plastic or restorative surgery, therefore, plays an important role in the management of these cases.

Bladder Neck Obstruction.—Bladder neck and posterior urethral obstructions generally fall into two categories; those in which the basic factor of obstruction is *neurogenic* in origin and those in which a *mechanical* defect causes the obstruction. The former seemingly are less frequent in children than in adults. Examples of the neurogenic group include children who have spina bifida occulta, meningoceles, cord tumors, or injuries to the spine resulting in paralyses of the lower extremities and loss of vesical and anal control.

A conservative program of therapy is usually employed in these cases with particular emphasis on the control of infection. Some of these children will develop either an automatic bladder or a semiautomatic type of bladder after a period of time with a minimal amount of urinary disability.

The types of obstruction most common in children have recently been listed by Campbell[1] as follows: contracture of the vesical outlet, congenital valvular obstruction of the prostatic urethra, congenital hypertrophy of the verumontanum (colliculus seminalis), ureterocele, prostatic lobes, and neuromuscular disease.

We find it difficult sometimes to distinguish between the first two, while the verumontanum seems proportionately large in relation to surrounding structures in most small boys and therefore difficult to label obstructive in all instances. We have seen a few cases of prostatic enlargment in children as well as ureteroceles large enough to obstruct the bladder outlet. The neuromuscular vesical disease group represents those which have been listed above as neurogenic in origin.

In both types of obstruction, the same serious complications, stasis and infection, are present, with renal insufficiency as the eventual outcome if these two factors are not combatted successfully. The mechanical obstructions are more amenable to surgical correction and therefore offer a better prognosis unless too far advanced.

Transurethral resection of bladder neck obstruction can be accomplished successfully using miniature instruments. The limitations imposed upon the procedure by the small size of the involved structures and by the small size of the instruments should again be noted. In our opinion it is wiser to proceed cautiously and with extreme consideration for these tiny structures at the risk of having to repeat the operation one or more times rather than to risk an operative failure by overzealousness at the beginning. We are more and more inclined to keep the bladder intact while this is being done, provided a satisfactory method of insuring adequate renal drainage can be maintained during this period. Retention catheters in the bladder do not always provide this assurance, particularly in very young children. They certainly do not provide adequate renal and ureteral drainage in some cases of hydronephrosis.

Cystostomy does provide adequate drainage in most instances and may be advisable if diverticula of the bladder requiring removal are present. On the other hand, scalpel removal of bladder neck obstructions via a cystostomy is

notoriously inaccurate and difficult. Cystostomy has the added disadvantage of delaying one's evaluation of the outcome of the bladder neck surgery until the bladder has again become a closed viscus. Furthermore, it has not been proved that an open, and therefore contracted bladder, may not in fact contribute additional obstruction of the ureters by the pressure of the thickened bladder wall upon the intramural portion of the ureter.

Hydronephrosis and Hydroureter.—Dilated ureters arise from a variety of causes. Unexplained dilatations of a severe degree are sometimes catalogued as megaloureter or congenital hydroureter. These are usually infected and as a rule the kidney and ureter are so badly damaged as to necessitate nephroureterectomy if the condition is unilateral.

Dilatation of the ureter due to mechanical causes falls into two general classifications, those due to extrinsic factors and those of intrinsic origin.

The former consist primarily of aberrant vessels and of fibrous or scar tissue bands, either of which may be encountered anywhere along the ureter, though more commonly found near the ureteropelvic junction. Either separately or in conjunction, they can produce sufficient pressure on the ureter from the outside to cause obstruction and dilatation above the point of obstruction with resultant stasis, infection, and renal damage.

Surgical removal of either offers an excellent prognosis if done before irrevocable damage to the structures above the point of obstruction has occurred. Otherwise, nephrectomy has to be done. In many instances the condition is associated with a constriction of the ureter at the point of obstruction so that we have an intrinsic factor of obstruction to contend with as well as an extrinsic factor.

Intrinsic obstruction implies a disturbance within the ureteral wall or lumen itself, such as stricture, constriction, stenosis, a foreign body such as stone, or, on occasion, a ureteral tumor.

It is in stricture or stenosis of the ureter that one has an opportunity to exercise all his ingenuity to relieve the obstruction yet preserve the continuity of the ureter. A wide variety of techniques for this purpose have been described. The chief handicap to a successful operation is the fact that many of these ureters have been stretched to almost tissue paper thinness which makes any form of plastic repair difficult and the prognosis unfavorable.

Regurgitation of the ureters is an interesting phenomenon both because of its frequency and because of the uncertainty regarding its origin. It is quite commonly observed in bladder neck obstructions and might be regarded purely as a back pressure manifestation except for the fact that it is frequently unilateral and furthermore is seen at times where no bladder neck obstruction is present. A patulous orifice also might suggest a purely mechanical origin for regurgitant ureters, yet regurgitation can occur with orifices that are not patulous and appear quite normal.

The fact remains that many dilated and regurgitant ureters regain their normal tonus and lose their dilatation if a bladder neck obstruction is successfully relieved. There does seem to be some relationship between the response

of the bladder wall and the response of the dilated ureter to an operation on the bladder neck, with both structures responding to about the same degree as a rule.

Anomalies of the Kidney.—The ordinary anomalies of the kidneys consist of single or polycystic disease, horseshoe kidneys, and ectopic kidney.

All of these conditions may be associated with infection and as a matter of fact pyuria is the presenting sign leading to their discovery in most instances.

The decision for or against surgical intervention in these cases, either in the presence or absence of infection, will depend upon one thing; namely, will surgery be helpful. Each case has to be handled individually.

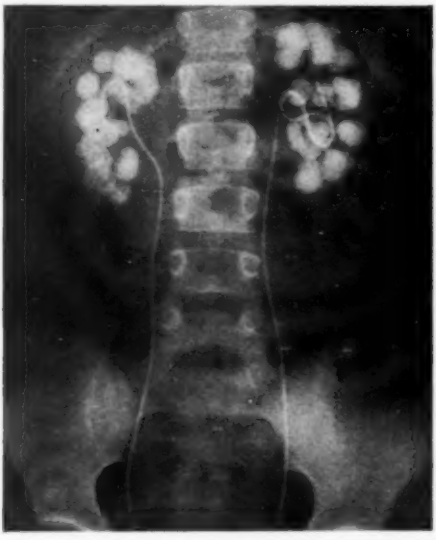

Fig. 5.—Plain plate of urinary tract with ureteral catheters in place. J. M., age 12; bilateral renal calculi.

Tuberculous and Calculous Disease of the Kidney.—It is not the intent of this paper to discuss either of these two conditions except in so far as infection is concerned and the part that surgery may play in the management of that infection.

We have seen very little renal tuberculosis in children without evident tuberculosis elsewhere. Should a proved unilateral renal tuberculosis be encountered, nephrectomy would have to be given serious consideration, as is the case in adult renal tuberculosis. It may be, however, that further experience with streptomycin in tuberculosis will warrant a nonsurgical approach in the future.

Calculous disease in children is more often a medical or metabolic problem than a surgical one, usually with an infectious background which further complicates and aggravates the picture. Both kidneys are usually involved

and whether the kidney substance itself is riddled with calcium material or the pelvis and calyces are full of stones, surgery is likely to be impracticable and of no avail. Infrequently a stone fragment may break away from the parent mass and become lodged in the ureter, necessitating surgical removal. For the most part these children need every bit of living kidney substance which they have so that, rather than risk further mutilation of the kidney by surgery, one's efforts are confined to the control of infection by chemotherapy and the correction of metabolic errors in so far as possible.

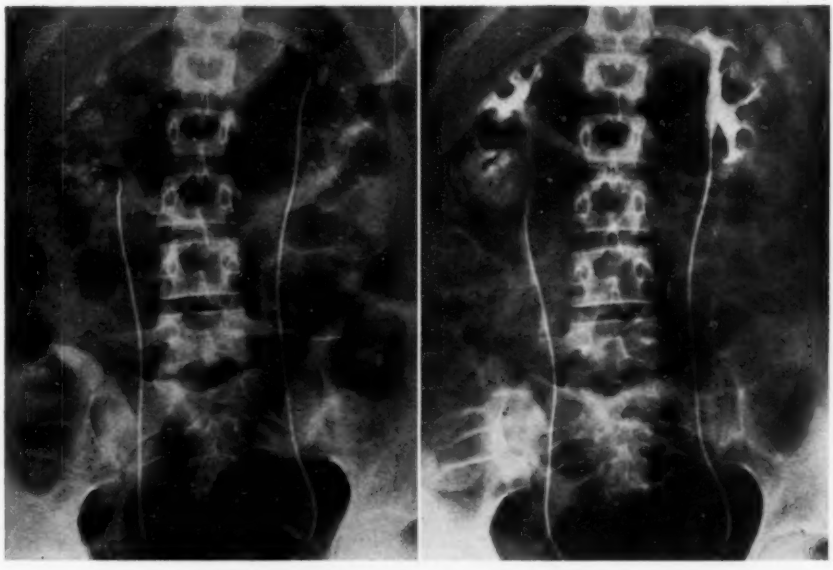

Fig. 6. Fig. 7.

Fig. 6.—Plain plate of urinary tract with ureteral catheter in place. R. B., age 13; bilateral nephrocalcinosis.

Fig. 7.—Retrograde pyelograms. Bilateral pyelograms on same patient as in Fig. 6.

Factors Influencing the Type of Surgery Employed.—No simple criteria are available which will serve to make this decision an easy one. The urologist is confronted constantly with the choice of sacrificing a kidney or the perhaps more difficult task of trying to repair it. The genitourinary structures of a child always exhibit amazing inherent reparative properties and this may be the determining factor in choosing a more conservative course in individual problems.

There must be reasonable assurance before a nephrectomy is done that the remaining kidney will support life. There must also be the same assurance that if a reconstructive or plastic procedure is done on the involved kidney, it will be able to resume its normal function after operation, free of stasis and free of infection.

We have had a few instances of unilateral kidney disease, with or without infection but with hypertension, where the latter was the determining factor in nephrectomy. It should be emphasized, however, that a kidney is not removed solely for hypertension. There must exist findings indicative or suspicious of unilateral involvement so that one would feel that removal of the kidney would constitute no loss to the patient but instead a probable gain.

On occasion a heminephrectomy or calycectomy can be done to remove a diseased portion of a kidney, retaining the nondiseased portion. This is particularly true where a stone is embedded in a calyx and the calyx both dilated and infected. Removal of the stone alone would leave behind an area of stasis and infection which would predispose to the formation of other stones.

Fig. 8.—Retrograde pyelograms. E. T., age 15; Unilateral hydronephrosis and hydroureter, left; hypertension; nephrectomy.

Gibson[2] in 1945 reviewed in detail the various technical procedures used in the repair of ureteral strictures and dilated kidney pelves. One of the most popular techniques is one in which an incision made downward along the course of the ureter through the strictured area is sutured across the course of the ureter at right angles to the incision. This is particularly adaptable to the stricture at the ureteropelvic junction associated with hydronephrosis.

As a rule no definite plastic procedure can be planned until the kidney or ureter has been exposed and the exact nature of the obstruction determined. Then, if a plastic repair is elected, one may either use a technique previously

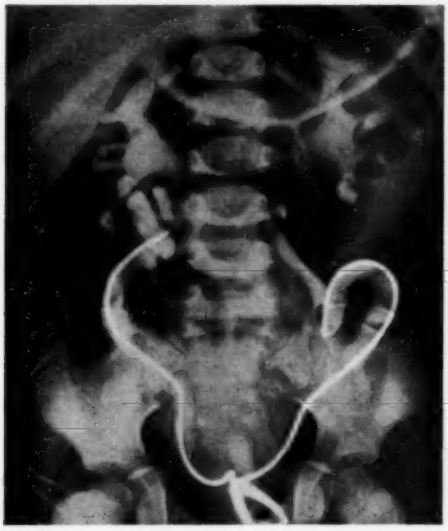

Fig. 9.—Retrograde pyelograms. W. F., age three; bilateral hydronephrosis with tortuous redundant hydroureters.

Fig. 10. Fig. 11.

Fig. 10.—Resection of redundant portion of right ureter with T-tube drainage and splint of ureter (same patient as in Fig. 9).

Fig. 11.—Same patient as in Figs. 9 and 10 after left ureter had also been partially resected and T-tube inserted.

known or he may improvise one to cover the situation which he has encountered. Two things must be kept in mind: to construct something that will be free of stasis when it has healed and to provide adequate drainage of the parts during the convalescent period.

A nephrostomy may have to suffice on occasion where it is imperative to get quick drainage of an infected kidney with the minimum of surgical shock. However, permanent or semipermanent nephrostomies have one disadvantage. The usual nephrostomy drainage tube is difficult to maintain in place and to keep functioning.

A dilated ureter is a good site for drainage in hydroureter and hydronephrosis and we are finding the conventional T-tube a very satisfactory drainage tube in this location. It remains in place well and its drainage properties, which are good to begin with, can be greatly increased by making additional perforations in the tube.

We are finding, as others have, that it is possible to resect considerable portions of long, dilated, tortuous ureters as a part of a reconstructive procedure. It is obvious sometimes that, regardless of what produced the hydroureter originally, the condition has reached a point where the ureter and its contents become of themselves an obstructive factor that must be dealt with. Removal of redundant sections of such ureters, end-to-end anastamosis of the severed ends of the ureter as in intestinal surgery, and drainage of the ureter at some point beyond the point of anastamosis with a T-tube, helps straighten out the ureter and at the same time provides excellent drainage during the convalescent period. We have removed as much as four inches of ureter in at least one case, and we have left T-tubes in place as much as five and one-half months after their insertion; their removal after this period entailed nothing more than simply pulling them out. The sinus tracts healed promptly.

Diversion of the urinary stream by means of a ureterointestinal anastamosis or ureterocutaneous transplant, with or without cystectomy, is undertaken in children much as in adults. The indications for this in children are found for the most part in congenital anomalies of the bladder, such as extrophy.

COMBINED USE OF CHEMOTHERAPY AND SURGERY

The drugs most commonly used at the present time as urinary antiseptics are the various sulfonamide derivatives, penicillin, streptomycin, mandelic acid, methenamine, and the various alkalinizing agents.

Most of these children who have an infection in the urinary tract associated with or secondary to some surgical anomaly are quite ill. They need every assistance that can be given. Certainly every effort should be made to combat the toxicity of their infection as well as to prevent the spread of infection to the other genitourinary structures.

The preoperative use of chemotherapy, therefore, is advisable in most instances and should be continued during the postoperative period as long as fever or pyuria persist. Care should be taken in the selection of the drug or drugs employed, but once a selection has been made, full dosages should be

used. A great many children have received inadequate chemotherapy before they come to urologic study and have developed a tolerance to the drug which militates against its effectiveness at the time when the greatest need for its effectiveness exists, namely, just before and after operation.

Too much should not be expected of any antibacterial agent, however, so long as a mechanical problem involving stagnation or stasis remains unsolved. The most potent aid which can be given drug therapy is the restoration of a normal current of urine through the urinary passages. In other words, if surgery was indicated and has been done successfully, one expects more of chemotherapy after surgery than before.

The author wishes to express his appreciation to Dr. A. F. Hartmann and Dr. D. K. Rose for their generous assistance in the preparation of this paper.

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Clinical Conference

CONFERENCE AT RAYMOND BLANK MEMORIAL HOSPITAL FOR CHILDREN, DES MOINES, IOWA

LEE FORREST HILL, M.D., CHIEF OF PEDIATRIC STAFF

DR. HILL.—This morning we have five cases to show you. The first three deal with problems of premature infants. Dr. Spevak, will you tell us about the first patient?

Case 1. Retrolental Fibroplasia

DR. JACK SPEVAK (Resident in Pediatrics).—This premature female infant weighed 2 pounds, 14 ounces at birth. During the pregnancy the maternal diet was adequate and the mother had no illnesses. Except for some minimal vaginal bleeding during the early stages of labor, there were no undue complications. At birth the infant was moderately asphyxiated, but color and respirations returned to normal shortly after she was placed in the incubator. There are two siblings who are perfectly normal.

The infant's course in the nursery was uncomplicated. A formula using powdered half-skim milk was used, and during the first week ascorbic acid, 50 mg., and vitamin D, 600 units daily, were begun. Lighting in the nursery is available from south windows and ordinary ceiling lights are protected by frosted globes. An ultraviolet air sterilization lamp is positioned over the entrance to the nursery but direct rays from this light source are screened from the infants. At no time during the baby's twenty-seven days of hospitalization were any ocular abnormalities noted. However, no ophthalmoscopic examination was done.

At the age of 5 months the infant was brought to the hospital because the mother suspected the baby could not see. The baby weighed 11 pounds, 5½ ounces, and was 21 inches in height. On examination of the eyes, the first finding was the characteristic searching movements of a blind child. The eyeballs appeared to be smaller than normal. No red reflex could be seen but an intense bilateral opacity was clearly visible with an ordinary flashlight. This opacity was thought to be lenticular, and a diagnosis of bilateral congenital cataracts was agreed upon. Later the infant was seen in consultation by the ophthalmologist at the State University Hospital at Iowa City, Iowa, who reported a diagnosis of retrolental fibroplasia.

DR. CHARLOTTE FISK (Staff Pediatrician).—Another premature infant born two or three days previous to this infant and weighing approximately 1,200 Gm. developed the same condition, but only in one eye. The baby's mother was diabetic.

DR. CHARLES L. BURR (Resident in Pediatrics).—This case is an example of one of the newer problems of the premature infant. It is an ocular maldevelop-

ment consisting of a persistence of hyaloid artery branches and the tunica vasculosa lentis. Later, it is believed, there occurs an overgrowth of embryonic connective tissue in the vitreous to cause blindness, usually bilateral. Clifford and Weller[1] report that 23 per cent of premature infants weighing 2 to 3 pounds at birth later developed retrolental fibroplasia. Many postulates have been advanced to attempt an etiologic explanation but as yet there is no proof for any. The two most popular at present are (1) precocious exposure of the premature infant to light, and (2) fetal anoxia. Warkany's experiments[2] with vitamin A deficiencies in rats suggest a relationship between retrolental fibroplasia and the maternal lack of vitamin A. However, Stewart Clifford reports the disease developing in premature infants who received 5,000 U.S.P. units of water-soluble vitamin A daily. In addition, one premature infant developed the disease who received the oral vitamin as mentioned and also a daily intramuscular injection of 20,000 U.S.P. units of vitamin A in oil.

The parents may be the first to notice that the infant does not see, for the manifestations first appear between 4 and 6 months of age. The searching nystagmus is often the outstanding characteristic first noticed. Further inspection may reveal one or several other characteristics of the disease; e.g., microphthalmia, shallow or absent anterior chambers, fetal-blue color of the irises, and an opacity occurring *behind* the lens. This latter point is stressed because we stubbed our toes at the first examination of the ocular opacities. Originally we had diagnosed bilateral congenital cataracts and were chagrined at not recognizing the condition earlier. However, a second choice diagnosis of retrolental fibroplasia was confirmed by the ophthalmologist.

In the sporadic unilateral cases occurring in the full-term infants, an erroneous diagnosis of retinoblastoma accounted for needless enucleations. Several types of treatment have to the present time been unsuccessful. Parents should be warned of the 5 per cent chance of glaucoma developing in this disease, as effective therapy for this complication is available.

Follow-up Note

This infant is now 9 months of age. Allowing two months for prematurity, the baby is still markedly retarded in its neuromuscular development. The head measures only 16.5 inches in circumference as compared with a chest circumference of 18.5 inches. In this case, then, the eye defect is associated with a cerebral defect.

Case 2. Anemia in a Premature Infant

DR. BRACE I. KNAPP (Resident in Pediatrics).—This 8-month-old white female infant was admitted to the hospital with the chief complaints of pallor and failure to gain weight for three months prior to admission.

The infant was delivered six weeks prematurely and was the second of a pair of twins, her twin sister being stillborn. Birth weight was 4 pounds, 6 ounces. The mother was anemic throughout her pregnancy, and was given liver extract weekly by injection and iron by mouth daily. Family history revealed a paternal aunt with severe anemia who had five miscarriages before the birth of a living child.

The infant was breast-fed for one month before being placed on an evaporated milk formula. She appeared to gain weight normally, weighing 13 pounds at 5 months of age. The mother noticed the infant's pallor soon after birth but was unconcerned because of the apparently normal physical and mental development. Since the age of 5 months she had become increasingly listless and apathetic, sleeping most of the time, showing little activity, and taking no interest in her surroundings. She had consistently refused both solid food and orange juice, although vitamin supplements had been maintained. Her weight on admission was the same as her weight three months previously, 13 pounds. Two severe upper respiratory infections occurred at 3 months and at 7 months of age. She was placed on iron three and one-half weeks prior to admission but no improvement had been noticed by the mother up to the time of admission.

Physical examination was essentially negative except for the marked pallor and listlessness. Neither the liver nor spleen was palpable. No petechiae were observed. Rectal temperature was 100° F.

Examination of the blood disclosed a red blood cell count of 2,580,000 with 4.3 Gm. of hemoglobin and a leucocyte count of 6,900 with 3 eosinophiles, 5 stab cells, 17 segmented cells, and 75 lymphocytes; there were 3 nucleated red blood cells per 100 white cells counted. Color index was 0.55. An hematocrit unfortunately was not obtained until after the first blood transfusion, which would make any volume index or mean corpuscular hemoglobin concentration calculated from such a value entirely inaccurate. For what it is worth, the value was 30 per cent. The blood smear showed pronounced anisocytosis with poikilocytosis with many hypochromic macrocytes and microcytes. There was considerable polychromasia and rarely a nucleated red cell was observed. The platelet count was 180,000; bleeding time, 1 minute, 45 seconds, clotting time, 6 minutes; clot retraction began in 45 minutes and was complete in 3.5 hours.

The day after admission a transfusion of 140 c.c. of whole blood was administered and at the time of presentation to this clinic the baby's appearance had already improved markedly.

DR. HILL.—This case is presented as an example of the problem with which one is confronted when a case of anemia in infancy presents itself for diagnosis. Since the report of Zuelzer and Ogden[3] on macrocytic and megaloblastic anemia was published, we have been on the alert not to overlook this possibility. While this case may well be one of iron deficiency anemia, nevertheless, other causes for the anemia should be carefully scrutinized. Dr. Knapp will discuss some of the differential points to be considered in some of the more common anemias of infancy.

DR. KNAPP.—In discussing the various types of anemias which may occur during infancy, it seems important in the diagnosis of this case to mention Diamond's classification briefly:

1. The normocytic normochromic anemias—including aplastic anemia, chronic hypoplastic anemia, and the anemia of prematurity.
2. The macrocytic hyperchromic anemias—pernicious anemia of childhood and the megaloblastic anemia of Zuelzer.

3. The microcytic hypochromic anemias—including iron deficiency anemia and the anemia of congestive splenomegaly.

4. The anemias associated with jaundice—hemolytic anemias, such as Cooley's anemia, congenital anemia, sickle cell anemia, and erythroblastosis fetalis.

In consideration of this infant's anemia the factor of prematurity is certainly present, but the anemia of prematurity usually develops during the second month after birth, reaching its greatest severity by the end of the third month. This infant's anemia, while probably present in the second and third months, did not influence her behavior and weight gain until 5 months of age. Diamond states that infants from mothers who themselves develop anemia late in pregnancy develop a profound anemia somewhat later, from the third to the ninth month. Hypochromic erythrocytes with a tendency toward microcytosis may be evident in the peripheral blood in the later stages but the hemoglobin rarely falls below 7.5 Gm. per 100 c.c. This infant's hemoglobin was 4.3 Gm.

Another type of anemia usually included in the normocytic normochromic anemias is that due to infection. A mixed type of anemia with both macrocytes and microcytes may be present, and once the foci of infection have been removed the anemia rapidly improves. This case, with a past history of infection, could easily fall in that category.

The macrocytic hyperchromic anemias are rare in childhood, but Blackfan and Diamond reported a series of fifteen patients between the ages of 4 and 16 months with anemias corrected by the parenteral administration of liver extract. Zuelzer[4] states the following criteria should be present before a diagnosis of megaloblastic anemia can be made:

1. The presence of a severe normochromic anemia, usually but not invariably macrocytic, with a wide spread in the corpuscular diameters. (This picture was certainly true in our infant. The hemoglobin in one of Zuelzer's cases was 5.7 Gm. This infant had a hemoglobin of 4.3 Gm.)

2. A tendency toward leucopenia and neutropenia with the presence of giant metamyelocytes and hypersegmented neutrophiles in the peripheral blood. (Neutropenia was moderately present in our patient but no metamyelocytes were noticed, although a few normoblasts were found.)

3. A diminution of platelets often associated with purpura or petechiae. (Platelets were only moderately reduced in our patient, appearing "numerous" on direct examination of the blood smear. No symptoms of capillary fragility were noted.)

4. An atypical bone marrow pattern, consisting of marked numbers of megaloblasts, although in the early stages there may be a pattern intermediate between normoblastic and megaloblastic erythropoiesis. (No marrow studies have been done at the time of this conference.)

Clinically, in megaloblastic anemia evidence of infection is usually present; the nutritional history is usually poor; weakness, pallor, loss of appetite, and irritability are present; splenomegaly is rarely found although the liver is usually increased in size. All of these symptoms are present in this infant and we will have to consider megaloblastic anemia very strongly in our differential diagnosis.

Since no jaundice was present in this case and no familial history of hemolytic anemia was given, the group of hemolytic anemias can be fairly well excluded. There is left, then, the anemia due to iron deficiency. The characteristic blood picture is one of a microcytic hypochromic anemia with the red blood count about 4,000,000 and the hemoglobin less than 10 Gm., usually between 4 and 8 Gm. A relative lymphocytosis is present (Not in our case!) but platelets are normal in number and no bleeding tendency is observed. The blood smear may show poikilocytosis, anisocytosis, and polychromasia, just as was reported in this case. The color index ranges from 0.40 to 0.80. (In this case it was 0.55.)

In conclusion, it would appear that the case presented fits either the picture of a megaloblastic anemia or an iron deficiency anemia, both of which are essentially "nutritional" anemias, and the presence of megaloblasts in the bone marrow would be the determining differential point.

DR. HILL.—Dr. Amick was in Buffalo at the area meeting of the American Academy of Pediatrics and heard Dr. Zuelzer give a paper on megaloblastic anemia in childhood. Dr. Amick, will you comment on this case?

DR. PERRY AMICK (Staff Pediatrician).—Dr. Zuelzer said the finding of only a few very large cells in the peripheral blood in a case of anemia is strongly suggestive of megaloblastic anemia. This can be proved by examination of the bone marrow, which shows many large megaloblasts.

Follow-up Note

Bone marrow studies were done the same day the case was presented in clinic and the following is the pathologic report: "The particles of marrow from the left tibia are very cellular and show an apparent predominance of erythropoietic tissue. This tissue contains a few megakarocytes. Eosinophiles are fairly numerous. Smears demonstrate a relative increase in normoblasts, while megaloblasts are not encountered. The granulocytes are not remarkable. In summary, there seems to be normoblastic hyperplasia of the bone marrow, secondary to hypochromic anemia."

The above report is fairly conclusive evidence that the infant's anemia was one due to iron deficiency and was not a megaloblastic anemia.

Iron in the form of ferrous sulfate was prescribed in a dosage of 7.5 grains daily. A blood count one month later was as follows: Red blood cells, 4,420,000; white blood cells, 14,000; hemoglobin, 12 Gm.; differential, 3 eosinophiles, 49 segmented cells, 44 lymphocytes, and 4 monocytes.

Case 3. Premature Infant Weighing Less Than 1,000 Grams

DR. J. B. SCHUNK (Assistant Resident).—The patient was a severely asphyxiated female newborn infant, delivered by a double footling presentation at 4:43 A.M. on May 8, 1948. The mother, a gravida vi, para ii, had been admitted to the obstetrical service three days previously with vaginal bleeding. The diagnosis of pregnancy was apparently in doubt. A Friedman test was attempted but the animal died. No fetal heart tones were heard. There was a history of three spontaneous abortions, all in the first and second trimesters with cause undetermined. Gestation had apparently been uneventful. Date of last

menstrual period was "sometime in September, 1947." Diet had been adequate with vitamin and mineral supplement.

She was discharged in twenty-eight hours and upon readmission both feet and lower legs of the baby were protruding from the vagina and she was delivered in a few minutes. The infant surprised the physicians by crying soon after delivery and was placed in the premature nursery. The color was deeply cyanotic and respirations were gasping and irregular. Precursory physical examination was otherwise negative.

Continuous oxygen, 3 to 4 L. per minute, was delivered by a hood. The upper respiratory passages were suctioned with a catheter. An effort to maintain body heat was made with hot water bottles and automatic regulation of the room temperature at 85° F. Humidity was controlled at 50 per cent. One milligram of vitamin K was given hypodermically. The infant was not handled except when absolutely necessary.

At 8 P.M. on the day of birth, a dark red discharge from the rectum was noted. The vitamin K was repeated. The rectal bleeding, mixed with meconium, recurred in small amounts during the following forty-eight hours, then ceased. On May 9, about thirty-eight hours after birth, 15.0 c.c. of normal saline was given subcutaneously and 15.0 c.c. of 5 per cent dextrose in distilled water was given by gavage. These feedings were repeated at six-hour intervals until late in the third twenty-four-hour period following delivery, when the infant showed good swallowing ability and feedings with powdered half-skim milk were begun in the amount of 7.2 c.c. offered every three hours with a soft, rubber-tipped dropper. At the same time 3⅓ per cent amino acid mixture was administered subcutaneously, 15.0 c.c. every eight hours.

The weight was obtained on the third day and found to be 889 Gm. (1 pound, 14 ounces).

The total cubic centimeters per kilo of body weight per twenty-four hours during the second, third, and fourth days was 67, 131, and 115, respectively. The caloric intake per kilo of body weight per twenty-four hours rose from 6.7 calories on the second day to 106 calories on the fourth day.

Sixty thousand units of penicillin as procaine penicillin in oil were given daily to combat infection.

The baby showed surprising vigor and had a good cry after the first day of life. With the strong swallowing reflex and promising clinical course, a favorable prognosis was hopefully made. However, on the morning of May 12, the fifth day of life, she suddenly began having apneic periods with deep cyanosis. Physical examination was negative. There was no respiratory obstruction, the lungs were clear, and the trachea in the midline. Alpha-lobeline, 0.5 c.c., was given hypodermically. Despite constant care and frequent use of artificial respiration, the infant expired at 8:20 P.M.

Consent for a post-mortem examination was given with the request that the head be excluded.

DR. HILL.—Dr. Davis, will you give us a report of the autopsy findings?

DR. S. K. DAVIS (Resident in Pathology).—This female infant presented few findings at autopsy that will aid much in the discussion. The weight was

810 Gm. and the baby measured 34 cm. crown to heel. Skin and sclerae demonstrated a mild icterus. There were no other external abnormalities. There was a small amount of xanthochromic peritoneal fluid. There were no abnormalities of the abdominal or pelvic contents in situ. The thoracic viscera were not remarkable aside from a rather marked venous engorgement of the large root veins and right atrium. The lungs were adequately inflated and showed no evidence of pneumonia. There were no abnormalities of the heart. The semifluid content of the jejunum and ileum was a foamy pinkish red. This was not present in other parts of the gut and no basis for the presence of blood could be ascertained. Examination of the brain was not permitted.

DR. HILL.—The survival rate of premature infants weighing less than 1,000 Gm. is about 10 per cent. Prematurity in itself is not an acceptable cause of death, except perhaps in the very small infants such as this one. In reviewing our management of this case we feel we may have been guilty of a common error —that of overdoing the fluid and food administration.

Approximately 50 per cent of the neonatal mortality rate occurs among prematurely born infants. Many of these lives could be saved with expert medical and nursing care. Providing the premature infant does not have a congenital defect inconsistent with life, escapes injury in the birth process, and avoids infection, his chances for survival should be good.

Dr. Schunk has prepared some remarks on the special hazards imposed by prematurity.

DR. SCHUNK.—During the sixteen-month period from January, 1947, through April, 1948, there have been 2,868 admissions to the newborn service of the Iowa Methodist Hospital. Of these, 210 or 7.3 per cent of the total were premature, weighing 2,500 Gm. (5½ pounds) or less. Of these, 36, or 17.1 per cent, have died, leaving a survival rate of 82.9 per cent.

The percentage of survivals of the various weight divisions of these premature infants was:

WEIGHT	ADMISSIONS	DEATHS	SURVIVAL (%)
2,001 to 2,500 Gm. (under 5 pounds, 8 ounces)	135	9	93.4
1,501 to 2,000 Gm. (under 4 pounds, 6 ounces)	41	7	82.9
1,001 to 1,500 Gm. (under 3 pounds, 5 ounces)	24	11	54.2
Less than 1,000 Gm. (under 2 pounds, 3 ounces)	10	9	10.0

These survivals compare favorably with anticipated percentages under good care that have been suggested by Dunham.

The handicaps of the premature infant's early existence are the inevitable result of the general immaturity of all the major systems. The proportionate increase in body surface and lack of subcutaneous tissue make maintenance of body heat difficult. The infant just discussed was kept in a premature nursery housing eight bassinets, with the obvious disadvantage of no ideal environment for any of the tenants. The frequency with which the premature infant displays irregular respirations and periods of apnea that may appear any time in the neonatal life reflects the inadequacy of the central nervous system. Convenient apparatus for the administration of oxygen, constant nursing care, respiratory

stimulants, and suction devices are valuable. Intermittent use of carbon dioxide-oxygen mixtures is sometimes recommended.

It would appear that the routine use of prophylaxis against infection is indicated in premature infants. Procaine penicillin in oil, administered in small daily doses, seems well suited for this purpose.

The tendency of the premature to develop acidosis has been repeatedly emphasized as one of the manifestations of inadequate renal function. Gordon has commented on the unreliable selective renal activity in utilization of sodium chloride solutions of the premature as compared with the full-term infant. The poor stores of vitamins with which the premature infant is equipped make early administration of supplements advisable. Especially is this true of vitamins C and K, which are given parenterally from the first day of life. Other vitamins are usually started on the fourth or fifth day.

There are other defects which the premature infant must combat: incomplete development of the enzyme system, hepatic immaturity, inadequate hematopoiesis, etc., all too much to discuss this morning. One phase of management, however, has been intentionally postponed to this point. The questions of when to inaugurate feeding, what food to use, and mode of administration, can be perplexing when suddenly foisted upon the physician. The feeding management of the very small premature infant has received little special attention in the literature. The infrequency of extremely small infants that give promise of survival does not seem to warrant a formal schedule, yet some sort of guide must be kept in mind. Overloading the infant with fluids and feeding mixtures in an effort to achieve early weight gain is perhaps the greatest hazard. The clinical appearance of the patient, of course, is the ultimate criterion, yet maintenance at an optimum is desired.

The first feeding should be after 48, possibly 72, hours of life. Feeding in the very small prematures should be by gavage and continued by that route until swallowing is possible without exhaustion after feeding. The total twenty-four hour intake must be carefully recorded and a gradual increase made to 160 c.c. per kilogram of body weight per twenty-four hours by the tenth to fourteenth day. The caloric intake can be increased at a slow rate also, reaching 125 calories per kilo in twenty-four hours at about the same time. Five per cent dextrose in distilled water may be offered in the first feedings with milk added in the second twenty-four hours of feeding. The proportion of milk to water may be gradually increased so that the feeding mixture is entirely milk by the tenth day. The addition of water to milk does not increase the digestibility of the milk, of course, but only tends to lessen the amount of milk taken. If smaller feedings are desired, the water portion of the feedings may be given subcutaneously as 2.5 per cent dextrose in water or 3⅓ per cent amino acids mixture. For the past several years we have been using a powdered one-half skim milk preparation (Alacta) as the food of choice for premature infants. This has been prepared as a mixture of 87 Gm. (10 tablespoons) of the powdered milk added to 600 c.c. (20 ounces) of water with 30 Gm. (1 ounce) of carbohydrate in the form of a dextrin and maltose preparation added. The percentages of total calories in protein, carbohydrate, and fat supplied by this food are, respec-

tively, 23.5 per cent, 57 per cent, and 19.2 per cent. This approximates the caloric distribution of the foods recommended by Gordon and co-workers[5] and by Powers.[6] The caloric content is about 0.81 calorie per cubic centimeter of feeding (approximately 22 calories per ounce). Although no planned study has been made, the general impression of our experience with this food has been very satisfactory. The Hess schedule has been used in this hospital for a number of years and has proved to be a useful and reliable guide. The workers already referred to have demonstrated large groups of patients with controls over long periods of time that have shown greater weight gains on half-skim milk than on other isocaloric feeding selections, including breast milk. The many arguments presented for the reduction of fat and increase of protein in the premature feeding are convincing.

Case 4. Primary Tuberculosis

DR. M. E. ALBERTS (Intern in Pediatrics).—J. C., a white female infant aged one year, 11 months, entered the hospital with the complaint of red "bumps" on the legs. These had first appeared one week previously on the right leg and two to three days later on the left leg. The child was seen by a private physician three days previous to her admission here, at which time there were several discrete, firm, red, tender, nonpruritic, ovoid nodules in the skin over the anterior tibial aspect of both legs, and one such lesion on the right buttock. These nodules were about 1 to 1.5 cm. in diameter and their long axis tended to lie in the longitudinal plane of the legs. A tuberculin test was done by the Mantoux method, using 1/100 mg. old tuberculin. A 3+ positive reaction was obtained.

At the time of admission to the hospital the nodules on the right leg were beginning to soften and presented the bluish-yellow color characteristic of a simple contusion.

The history of the patient revealed contact with a man who has untreated tuberculosis. The child's parents manage a tavern and maintain their home in the rear of the same building. The child, therefore, comes into close contact with the patrons of the tavern, and has had especially close contact with the man in question. The parents of the child state that the same man is held responsible for another person becoming infected with tuberculosis . . . that person is now being treated in a local hospital. Careful inquiry uncovered no other possible source of tuberculous infection. Both parents are having chest x-rays made at the present time.

The past history of the child reveals nothing of significance. She has had occasional colds, had thrush three months ago, and during the first year of life had roseola infantum. Her birth weight was 7 pounds, 4 ounces; her present weight is 24 pounds, 4 ounces.

Physical examination is essentially negative with the exception of the nodules in the skin. The lungs are clear anteriorly and posteriorly to auscultation and percussion. However, x-ray of the chest reveals a patchy pneumonia extending from the right hilus to the diaphragm in the medial half of the right lung. The rest of the lung fields are clear (Fig. 1).

The laboratory findings are as follows: red blood cells, 4,230,000; hemoglobin 11.8 Gm.; white blood cells 14,750 with 68 per cent polymorphonuclear cells, 31 per cent lymphocytes, and 1 per cent monocytes. The blood sedimentation rate (Wintrobe) was 100 mm. in one hour. Gastric washings for acid-fast organisms have been negative on three occasions. Stool examination for acid-fast organisms has also been negative. A guinea pig has been inoculated with some of the concentrated gastric washings. Kline and Kahn tests are negative.

The patient's course in the hospital has been afebrile, although the temperature does show fluctuation of a nonspecific nature. She has been receiving streptomycin, 1.0 Gm. per day, in divided doses.

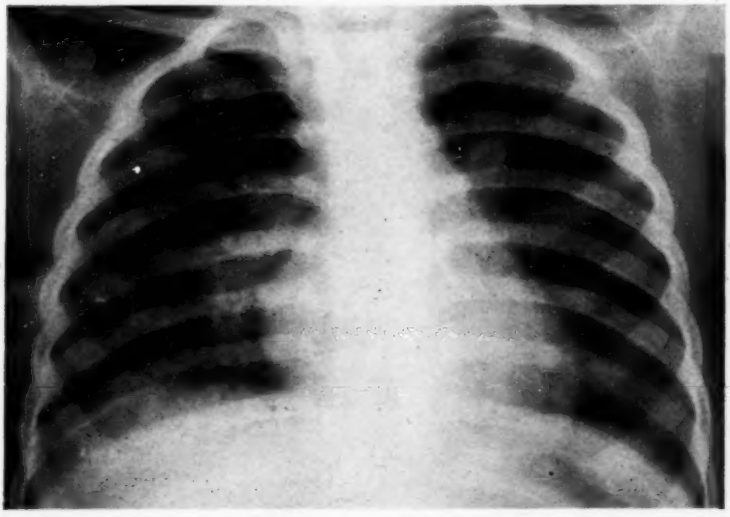

Fig. 1.—Film taken before streptomycin therapy shows pneumonic shadow in right hilus.

Dr. Hill.—The lesions on the legs of this child were typical of erythema nodosum. The most common underlying causes of erythema nodosum in children are primary tuberculosis and rheumatic fever. However, rheumatic fever is unlikely because of the patient's age. Primary pulmonary tuberculosis, including both the parenchymal and lymph node components, can seldom be diagnosed by physical examination alone. As in this case, diagnosis rests upon the reaction to tuberculin and upon the x-ray. Even after we had seen the x-ray film and had gone back over the right lung meticulously, no abnormalities could be detected.

This is the first case of primary tuberculosis in the acute stage that we have seen in this hospital since streptomycin became available. Whether or not to use the drug for J. C. was debated at some length. In the great majority of children the lesions of primary tuberculosis retrogress over a period of months

and finally calcify or even disappear altogether. However, in the first four years of life, and especially in infancy, progression from the primary complex may occur and give rise to such fatal forms of tuberculosis as miliary tuberculosis, tuberculous bronchopneumonia, and tuberculous meningitis. In the event that any of these forms emerged in this patient, streptomycin would certainly be employed. It seemed reasonable, therefore, to consider the use of streptomycin from a preventive point of view (prevention of the fatal forms). For this purpose a relatively small dose, given over a shorter period of time, might suffice. Objections to streptomycin include the danger of damage to the eighth nerve and to the vestibular apparatus, and the less substantiated risk that a resistant organism might emerge which, if communicated to others, would give rise to tuberculous disease not susceptible to drug therapy. Since danger of spread in primary tuberculosis is minimal anyway, the latter objection did not seem too important.

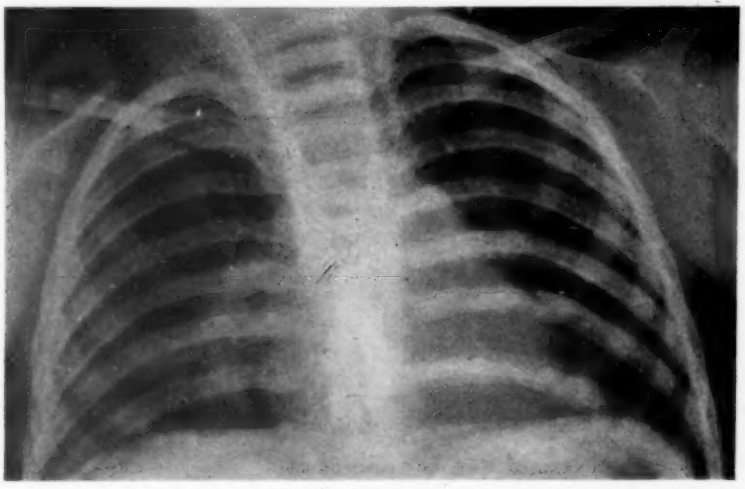

Fig. 2.—Film taken approximately one month after one week of streptomycin therapy. Shadow essentially unchanged.

We should have liked to have kept our patient on streptomycin for two weeks, but we had to be content with seven days. The sedimentation rate taken at the end of this period had dropped from the original 100 to 40 mm. in one hour. The nursing staff reported the child had become much more active and that her appetite had improved greatly. A repeat x-ray film of the chest, however, showed no essential change in the parenchymal lesion.

Another observation we had hoped to make was the effect of streptomycin on the tuberculin reaction. Presumably, if the drug could be given to the point of destruction of all tubercle bacilli, a positive reaction would change to a negative one. Obviously, the period of streptomycin administration in this case was too short to permit of any conclusions. However, a repeat test was done with

the same preparation of old tuberculin and with the same dosage (1/100 mg.). The resulting reaction, while positive, was approximately one-half the size of the original reaction.

Follow-up Note

The sedimentation rate one month later was still 41 mm. in one hour. The roentgenogram (Fig. 2) was essentially unchanged. A third tuberculin test with 1/100 mg. old tuberculin gave a positive reaction approximately one-fourth the size of the original test. The child had gained 1.5 pounds in weight and was symptom free.

Case 5. Salicylate Intoxication

Dr. R. J. Byrum (Assistant Resident in Pediatrics).—This 9-year-old white boy, weighing 72 pounds, had a six-day history of migratory joint pain and joint swelling associated with a low-grade fever prior to admission. No history of recent respiratory infections or past rheumatic manifestations could be elicited. Examination revealed a febrile (102.4° F.), acutely ill boy whose pharynx was moderately inflamed. His left cardiac border seemed slightly enlarged to the left, and though no murmur could be heard there was an accentuated second sound over the aortic area. The right ankle and left knee were moderately swollen, warm, and extremely tender to palpation.

Laboratory data included an erythrocyte count of 3,520,000, hemoglobin 12.6 Gm., and a leucocyte count of 10,400 with a differential of two eosinophiles, 4 stab cells, 58 mature polymorphonuclears, and 36 lymphocytes. The sedimentation rate (Westergren method) was 111 mm. per hour. Urinalysis, Kahn and Kline, and Mantoux tests were negative. A roentgenogram of the chest was interpreted as revealing a normal heart size, but the cardiac configuration suggested a mitral valve lesion. The electrocardiogram showed a prolonged P-R interval.

After making a diagnosis of rheumatic fever, 60 grains of sodium salicylate daily were ordered. Due to an error, additional salicylates were given in the form of acetylsalicylic acid, grains 30 daily, to make a total of 90 grains of salicylate administered daily. The symptoms rapidly improved and the arthralgia had subsided by the fifth hospital day. On the evening of the sixth day the patient became confused and began to develop hyperpnea and restlessness. By the following morning he appeared slightly cyanotic, complained of a headache, was mentally confused, and respirations continued to be deep and pauseless. There was no fever. Slight nuchal rigidity and dryness of the mucous membranes were also noted. A carbon-dioxide combining power was 31 volumes per cent and a blood salicylate level of 40 mg. per 100 c.c. (400 gamma) was obtained.

Oxygen was immediately begun, all salicylates were discontinued, and intravenous fluids were ordered to hasten urinary excretion of the drug. One ampule of Synkamin and 100 mg. of ascorbic acid daily were also added as prophylactic treatment of a possible prothrombin disturbance. Two days later the salicylate level was 12 mg. per cent and the child was much improved. Hyperpnea was no longer present and he appeared bright and alert. Because of the still elevated

sedimentation rate of 115 mm. per hour, sodium salicylate (60 grains) was again instituted, but was decreased to 45 grains two days later when a salicylate level of 29 mg. per cent was obtained. Since that time the patient has been maintained on that dosage with no further toxic manifestations.

DR. JOE M. STANDEFER (Staff Pediatrician).—The relatively recent popularization of massive salicylate therapy in rheumatic fever has, no doubt, increased the number of salicylate intoxication cases. With this increase there has developed a finer understanding of the mechanisms involved in this dramatic symptom complex.

Salicylates have been used for many years to alleviate the symptoms of the common cold and rheumatic fever. It has long been known that infants under one year of age tolerated aspirin very poorly and it has recently been emphasized that younger children could not tolerate doses of salicylates thought to be safe for adults; namely, 0.13 to 0.19 Gm. per kilogram of body weight daily.[7] It has recently been shown that aspirin produces toxicity more readily than sodium salicylate in young children.[8]

The signs of salicylate toxicity are: (1) hyperpnea, which is deep and pauseless and comparable with the hyperpnea of diabetic acidosis; (2) apathy and lassitude; (3) anorexia, which may be severe; (4) tinnitus; (5) dizziness; (6) irritability and restlessness; (7) disorientation, stupor, and convulsions; (8) thirst; (9) sweating; (10) fever, which may be high; (11) abdominal pain; (12) pallor and cyanosis; (13) epistaxis and hemorrhagic phenomena; and (14) dehydration.

The laboratory findings which confirm salicylate intoxication are: (1) increased prothrombin and coagulation times and an elevated blood chloride level; (2) urinary findings; e.g., (a) reduction of copper by salicylate compounds, (b) positive Gerhardt's test, (c) acetone and diacetic acid, and (d) albumin, casts, white and red blood cells indicating renal damage; (3) salicylate blood levels over 32 and commonly over 40 mg. per cent; (4) the pH of the blood is initially elevated; later the pH may be reduced with an associated acidosis; and (5) the carbon-dioxide combining power alone is unreliable in salicylate intoxication. It may be normal or depressed even with an elevated pH of the blood. However, if values for both the carbon-dioxide combining power and pH of the blood are available, they provide valuable information to guide in giving correct therapy.

MECHANISM OF SALICYLATE INTOXICATION

The mechanism responsible for the development of respiratory alkalosis in salicylate intoxication is hyperventilation. The hyperventilation or hyperpnea is deep and pauseless, and is probably due to a disturbance in the respiratory center. As the hyperventilation progresses there is a loss of carbon dioxide from the alveoli of the lungs which is followed by a loss of carbon dioxide from the blood. This causes a derangement of the $HHCO_3$: $BHCO_3$ ratio in that the $HHCO_3$ is diminished. Unless compensated by a decrease in the $BHCO_3$, the ratio 1:20 is decreased, the pH rises, and an uncompensated alkalosis results.

To compensate for the abnormal loss of carbon dioxide through the lungs, there has to be a loss of $BHCO_3$. This is thought to be accomplished by an increase in the chloride ions. The increased chloride retention diminishes the residual base present for combination with HCO_3^- to form $BHCO_3$. It is thought by some that the kidneys preferentially excrete HCO_3^- over Cl^- to accomplish this task.

Some investigators have also noted that there is an increase in plasma lactic acid and ketone bodies which further reduces the $BHCO_3$ and promotes a more normal pH. An overcompensation of this mechanism would lead to the development of an acidosis as has been reported. As hyperpnea would also be present in this condition, it is evident that the pH of the blood must be known before treatment with alkalies is instituted.

Since the bulk of the salicylates are excreted in the urine, the treatment is directed toward increasing the renal output. Another factor to be considered in the treatment is the administration of the chlorides for union with the base present. Both of these can be accomplished by the administration of adequate amounts of glucose in normal saline. Oxygen administration as well as other supportive measures should be followed out. Morphine or barbiturates have been used by some to slow the respiratory rate and thus diminish the loss of carbon dioxide from the lungs. Vitamin K and ascorbic acid are used to diminish the hemorrhagic manifestations.

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Psychologic Aspects of Pediatrics

MENTAL TESTING IN CHILDREN

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PSYCHOLOGIC testing, originally developed by Binet in 1905 to measure mental capacity, has been greatly extended within recent years and tests are now available for measuring innumerable psychologic attributes. Thus there are tests for measuring emotional stability, emotional interests, masculinity-femininity, social intelligence, honesty, social attitudes, scholastic interests, special abilities, educational achievement, and various personality traits. The tests which are of special interest to the physician are those which relate to mental functioning.

Psychologic testing of children should be discouraged except where a specific indication exists. There is no more reason for determining the intelligence quotient in a normal child than in estimating the basal metabolic rate, and there are disadvantages. A numerical rating of intelligence has only relative accuracy. By permitting seemingly precise comparisons, it encourages an attitude of competition among mothers and may lead to needless parental concern, disappointment, and anxiety. There are, however, occasional instances of doubtful intelligence where testing is indicated. The physician should therefore familiarize himself with the uses and limitations of this technique. He should be able to interpret the results of tests in a general way and understand the degree of reliability and validity with which these interpretations are made.

INDICATIONS FOR MENTAL TESTING

1. *Doubtful Intelligence.*—Intelligence testing is useful in detecting retarded mentality in doubtful cases. In addition, it gives a measure of the extent of the deficiency and shows how it affects the child's adjustment in other respects. Children who make little use of their capabilities because of emotional blocking and who are, as a result, erroneously considered to be defective can be recognized in this way.

2. *Behavior Problems.*—Where the difficulty appears to be an outright behavior problem it is often desirable to have an appraisal of the child's intellectual status in order to ascertain whether this factor is aggravating the total behavioral picture.

3. *Educational Retardation.*—In appraising a child who is doing poorly at school the relationship between all factors complicating the patient's adjustment should be made. This includes testing not only for intelligence but for special disabilities (reading, arithmetic, spelling, etc.) and personality as well.

4. *Diagnostic Problems.*—Mental testing is helpful in differentiating mental deficiency per se from that associated with organic defect, a psychosis, or a com-

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bination of these. For this purpose intelligence tests should be supplemented by personality tests. Feeble-minded children score uniformly low, i.e., the retardation in mental development is widespread, relating to all the mental faculties. Where the mental defect is organic or psychotic in origin the scatter of test results is likely to be wide. For example the child may be able to give only a 4-year response on certain tests but on others may score 8 or 10 years.

5. *Effect of Therapy.*—Mental testing is helpful in offering a baseline against which the effects of various types of therapy, such as educational tutoring, medication, e.g., glutamic acid, benzedrine, hormonal therapy, (as thyroid extract) or psychotherapy can be measured.

6. *Miscellaneous Uses.*—Mental testing has been found useful in child adoption, vocational guidance, in the appraisal of aptitudes, in work with juvenile delinquents, in the investigation of mental growth, in research on individual differences, and in the study of the relation between intellectual and personality factors and physical handicaps, as poor vision, poor hearing, disturbances of the nervous system.

In mental testing the individual's performance in many different functions is measured. Failure or success in any one mental function may be of only slight significance for classifying an individual, since correlation between the mental functions varies widely. Success in music, representative drawing, and mechanical ability, for example, are relatively independent and correlate poorly. On the other hand, reading ability and aptitude in arithmetic are fairly closely but not perfectly correlated with general competence, while spelling is not readily predictable from general school grading.

Mental testing cannot be expected to measure pure native capacity for intellectual accomplishment. It indicates the immediate efficiency of the individual in certain specific respects. The results of intelligence tests are relative, i.e., the score which the child makes has significance only by comparison with the scores of other children on the same test. The score serves as an indication of the rank of the individual in a group in which he may be placed or with which he may be compared. What is being measured is the reaction of the innate endowment of the child to his training at the moment when he is being tested. The particular activities demanded of the individual being tested are selected from those which are likely to be common to the experience of all the persons who are to be compared.

Like other laboratory procedures, psychologic tests depend for their reliability not only on the accuracy with which they are standardized but also on their proper administration, scoring, and interpretation. In addition, the wholehearted cooperation of the child being tested must be obtained and the subject must be representative of the populations used originally in standardizing the test in regard to age, sex, educational level, and cultural background.

Norms for intelligence are based upon the child's ability to perform prescribed tests in a prescribed manner at certain stated ages. By mental age is meant "that degree of general mental ability which is possessed by the average child of corresponding chronologic age" (Terman). The score obtained by

adding up credits which the child received for all age levels is referred to as the mental age (M.A.). The ratio of mental age to chronologic age (C.A.), multiplied by 100, gives the intelligence quotient (I.Q.) The basal age (B.A.) is the highest age level at which all the tests are passed. The table below gives the range of intelligence quotients in children of a "normal" population.

RANGE OF INTELLIGENCE QUOTIENTS IN CHILDREN

	I. Q.	PERCENTAGE IN POPULATION	CLINICAL DIAGNOSIS
Inferior intelligence	Below 70	1	Mentally deficient
	70- 79	5	Borderline
Normal range	80- 89	14	Dull
	90- 99	30	Average or Normal
	100-109	30	Average or Normal
	110-119	14	Bright
Superior intelligence	120-129	5	Very bright
	130 and over	1	Gifted
	150 and over	0.1	"Genius"

The average I.Q. is close to 100 with a standard deviation of 16 points. The error in the usual test is about 5 points either way.

The limitations of the I.Q. are as follows:

1. Its validity does not extend beyond the validity of the scales used.
2. It does not take into account special abilities or disabilities.
3. It may put a premium on certain abilities depending upon the test used.
4. Caution is necessary in interpreting intelligence test scores since different tests may yield different results, while the subject's relative position on the normal curve remains undisturbed. That is, a subject's clinical diagnosis may alter on the basis of an I.Q. computed as a result of findings, but his actual capacity has not changed. One test may stress memory, another comprehension, and a third verbalization, so that the child will score higher on the test which emphasizes his own special abilities. It is erroneous to assume that an I.Q. obtained on one test will be identical with the I.Q. obtained on another and therefore the test administered must always be considered.

TYPES OF MENTAL TESTS

Mental testing was introduced by Alfred Binet in 1905. With his co-worker, Simon, he submitted a large number of questions and tasks to children of various ages and capabilities. By the simple yet original device of grouping the tasks according to age, he was able to estimate the mental capacity of children from the number of tests which were successfully performed at each age level. Since Binet's time the tests have been simplified. At present the revision of the Stanford-Binet test, introduced by Terman and Merrill[1] in 1937, is most widely used.

Terman and Merrill Revision of the Stanford-Binet Scale (1937).—This test is designed to measure various mental faculties such as memory, reasoning power, judgment, grasp of general information. Thus, children at 2 years of age are expected to be able to insert insets (a square, circle, and triangle) into a form board; to identify certain objects by name such as a button, a thimble,

a cup, and the like; to identify various parts of the body; to build blocks, etc. Later on, for example at 5 years, the child is expected to complete an incomplete drawing of a man; to fold paper in the form of a triangle; to give simple definitions of words such as "ball," "hat," "stone"; to copy a square; to memorize sentences, etc. At 10 years, the child should be able to define certain words; he should be able to recognize absurd situations in pictures which are shown to him; he should be able to repeat six digits, etc.

Wechsler-Bellevue Adult and Adolescent Scales.—The tests developed by Wechsler[2] are suitable for subjects ranging in age from 10 to 60 years. The scales are divided into ten subtests, five verbal, yielding a separate Verbal I.Q. and five nonverbal yielding a Performance I.Q.; the two scales combined furnish the examiner with a General I.Q. The verbal scale consists of general information items; a comprehension test consisting of questions such as, "Why should people pay taxes?" "Why are laws necessary?" arithmetical reasoning problems ranging from simple addition to more complex calculations like: "If a train goes 150 yards in ten seconds, how many feet can it go in one-fifth of a second?"; a test of similarities wherein the subject is asked to state in what way two things are the same or alike, e.g., orange—banana, coat—dress, etc.; and a memory for digits test, in which the subject's ability to repeat various sequences of digits forward and backward is tested. The Performance Scale consists of a completion test wherein the subject points out an important deletion from a series of fifteen pictures; a picture arrangements test consisting of several series of cartoonlike pictures which are presented to the subject in a mixed order which he has to place in correct sequence; an object assembly test which presents the subject with three separate dismembered items which he has to put together properly; a block design test which presents different designs which the subject has to duplicate with colored cube blocks; and a digit symbol test which requires the subject to substitute symbols for numbers from a code consisting of nine numbers each with a different symbol.

The chief advantages claimed for the Bellevue Scales are:

a. The material is well-suited for the testing of adolescents and adults.

b. An individual's performance is compared with the average of his own age group.

c. The full scale gives appropriate weight to performance and verbal tasks.

d. The test results agree better with clinical judgments than those obtained from other general intelligence tests.

e. The test is an aid in diagnosis since factors that may be contributing to emotional maladjustment can be uncovered. Thus, this test not only offers objective quantitative results but it is useful qualitatively as an aid in differentiating between "normal," psychoneurotic, psychotic, and organically determined behavior.

The Bellevue Scales have been administered extensively to both children and adults. Because of their construction and statistical bases the I.Q.'s which they yield are often in variance with the I.Q.'s obtained for the same subject whose Binet I.Q. is known. Weider, Levi, and Risch[3] have constructed tables

that equate the two I.Q.'s and show that the subject's relative position does not change although the I.Q. designating this position results in a different numerical figure.

Testing During the First Two Years.—Intelligence during the first few years of life cannot be as accurately measured as at later ages but tests have been devised by which infants may be classified as backward, dull normal, average, or advanced.[4] Since tests in infants are largely dependent on motor ability, a careful physical examination with particular attention to muscle tonus and coordination should precede the tests. The difficulty in recognizing spastic diplegia and basilar ganglion lesions in young infants is well known. Myatonias which interfere with motor performance are occasionally seen. Estimates of intelligence in infants with mild or even moderate degrees of hydrocephalus should be made with caution.

Testing during early life is useful where adoption is contemplated and this procedure is now used by many agencies. The tests require more time and practice than most physicians are able to devote to them; nevertheless we should be acquainted with the character of the tests used and with the reliability of the results. The tests frequently applied in office practice such as the age of smiling or sitting up are of little value because they are not standardized and the normal variability is wide.

In 1925 Gesell[5] published his Developmental Inventories, which established norms for mental and motor growth during the preschool period. More recently, Gesell and Amatruda[6] published a more complete developmental schedule from four weeks through five years. The tests reveal not only mental retardation but emotional instability, defects in vision, in hearing, and in motor ability. The effects of cerebral injury can be distinguished from signs of amentia within the first year.

According to Gesell practically every case of mental deficiency can be recognized in the first year of life except for the small number of exceptional cases arising from secondary causes later on. This is best done by a progressive appraisal of the child's maturity status from time to time. The criteria used by Gesell are the young child's command of his body postures in the supine, prone, sitting, and standing positions; his ability to roll, creep, walk, and run; his discriminating regard for sights and sounds; his ability to grasp, manipulate, and release objects; his ability to exploit his environment in a varied and increasingly elaborate manner; his propensity to learn and profit by experience; his power to communicate with his social environment by visual following, by intent and regard, by gestures, vocalizations, and words; his discriminating regard for persons; his capacity to assimilate the culture into which he was born.

The Gesell tests are designed to disclose the four basic fields of behavior: motor, adaptive, language, and personal-social behavior. The results are expressed as D.Q. or Developmental Quotient, rather than as I.Q. The D.Q. is the ratio between the maturity age and the chronologic age. Gesell considers the D.Q. more discriminating than the I.Q. since the D.Q. can be specifically ascertained for each field of behavior and for individual behavior traits.[7]

Goodenough Draw-A-Man-Test[8].—This test is simple to administer, it requires no special material and it generally holds the child's interest. Moreover it is possible to learn much about a child's problems from his drawing and from his own interpretation of it.

The examiner asks the child to draw a man. He is urged to draw it carefully, in the best way he knows how and to take his time. The test is highly reliable, correlating well with the Binet tests. The test is most suitable for children between 3 and 10 years of age.

The child receives one point for each of the items which is present in his drawing. For each 4 points one year is added to the basal age which is 3 years. Thus if the child's drawing shows that the first nine items are present in his drawing he scores 9 points and his mental age score is 3 plus $\frac{9}{4} = 5\frac{1}{4}$ years.

Method of Scoring the Goodenough Draw-a-Man Test:[8]

1. Head present.
2. Legs present.
3. Arms present.
4. Trunk present.
5. Length of trunk greater than breadth.
6. Shoulder indicated.
7. Both arms and legs attached to trunk.
8. Legs attached to trunk and arms to trunk at correct point.
9. Neck present.
10. Outline of neck continuous with that of head or trunk or both.
11. Eyes present.
12. Nose present.
13. Mouth present.
14. Both nose and mouth in two dimensions; two lips shown.
15. Nostrils indicated.
16. Hair shown.
17. Hair on more than circumference of head, nontransparent, better than scribble.
18. Clothing present.
19. Two articles of clothing, nontransparent.
20. Entire drawing, with sleeves and trousers shown, free from transparency.
21. Four or more articles of clothing definitely indicated.
22. Costume complete without incongruities.
23. Fingers shown.
24. Correct number of fingers shown.
25. Fingers in two dimensions, length greater than breadth, angle subtended not greater than 180 degrees.
26. Opposition of thumbs shown.
27. Hand shown as distinct from fingers or arms.
28. Arm joint shown. Either elbow, shoulder, or both.

PERFORMANCE TESTS

The usual mental tests depend to a large degree on the ability of the child to understand language and to respond orally. Children who are deaf, retarded in the development of speech, or mute, illiterate, or from a home where a foreign

language is spoken are consequently at a distinct disadvantage in the ordinary test. To overcome this difficulty a number of performance tests have been devised which require little or no language ability.

In 1931, Stutsman[9] published the *Merrill Palmer Performance Tests,* which include tests from 18 to 72 months arranged in six-month groups. These have the advantage over most tests at the preschool level (2 to 3 years) of keeping the child interested. They have a high degree of reliability.

Of considerable value is the *Pintner-Paterson Performance Test*[10] which is suitable for children of 4 to 15 years of age. It includes a great variety of tests and requires very little verbal response. Though it tests facets of mental abilities in a manner different from that used by the Binet tests, it nevertheless correlates closely with the Stanford-Binet intelligence scores.

The *Arthur Point Scale of Performance Test*[11] has also enjoyed wide popularity as a performance test where testing with the Binet is either not possible or unreliable. It was first published in 1925 and is most useful for ages 5 to 15 years. As the name suggests, it is primarily a point scale and heavily weighted with manual tasks. It, too, correlates well with the Binet results.

The test is made up of a number of subtests among which is the Sequin Form Board which has insets for ten geometric figures of different shapes. The subject is allowed three trials to fit the figures into the board. The score is the time of the shortest trial. Another is the Healy Picture Completion Test. For this test there is also a kind of form board consisting of a large picture from which ten square holes have been cut. The subject is supplied with fifty pictures of objects pasted on blocks and is expected to insert blocks into the appropriate squares.

TESTING FOR HANDICAPPED CHILDREN

The Binet-Simon Test has been especially restandardized for application to the blind[12] as well as to the deaf.[13] In the former case the visual material has been modified and adapted for tactual stimulation, and in the latter case pantomime and visual rather than auditory stimulation is used. Whenever possible, performance tests of intelligence and other nonlanguage tests which minimize the need for verbal directions are appropriate for administration to the acquired deaf patient, the mute, the retarded, the reading disabled, the bilingual, and the child from a different culture with difficulty in comprehending the instructions as presented.

GROUP TESTING

Though not new at the time, group intelligence testing developed as a useful instrument from the work done in the U. S. Army during World War I. The Army Group Intelligence Examination Alpha, generally referred to as Army Alpha, consisted of questions designed to measure auditory attention; simple arithmetic problems; items involving common sense or practical judgment; pairs of words to be marked as having the same or different meaning; disarranged sentences to be comprehended and marked true or false; incomplete number series to be completed; verbal analysis; and items calling for general information.

The army tests were found useful in the selection of soldiers and officers for various duties, for advancement and for special training. It served as a ready means for the early identification and elimination of those unfit for military service because of low intelligence.

Numerous revisions of the original army test have been devised and new types of group tests have been introduced for various populations and situations. These group tests are easier to give, they can be machine-scored, and they can be administered to large groups at the same time by practically untrained persons. They have been used in military organizations, schools, industry, civil service, prisons, and the like.

SOURCES OF ERROR

In order to obtain reliable information from an intelligence test certain criteria must be met:

(1) The wholehearted cooperation of the child must be obtained, otherwise the score will be too low. This occurs also if the child is fatigued, ill, or unmotivated.

(2) The instructions must be followed rigidly by the examiner.

(3) The technique of scoring must be closely adhered to. Special psychologic training is necessary for the administration of tests and for the interpretation of results. Some of these tests are scored by grade or by percentile ranking rather than by I.Q., thus making interpretations more complex and requiring extra caution.

While a numerical rating is helpful in many situations, a qualitative appraisal of the results yields significant information which should be taken into consideration. Such factors usually shed light on the child's behavior, thought processes, social, emotional, and interpersonal relationships with parents, siblings, and school chums. While these latter factors are more reliably ascertained through the use of procedures specifically designed for these purposes (tests of personality), observation and attention to the child's approach to material, conversation, cues, etc. yield valuable information during intelligence testing.

At best, intelligence tests merely sample a few aspects of the complex, multidetermined human factor which we call intelligence. The objective character of the results obtained enables comparisons to be made with norms that have been standardized. While this procedure is far better than a subjective, biased, unstandardized appraisal, caution must be exercised not to overemphasize the quantitative features of the I.Q.

FACTORS INFLUENCING INTELLIGENCE TEST RESULTS

Sex has only a slight influence on the mean scores, but boys are somewhat more variable than girls. Children of superior social status average considerably above children from an inferior environment. The order among siblings appears to affect the I.Q. only in so far as first-born children rank as gifted children more often than later-born. Superior intelligence is uncommon in twins. Bilingualism has little effect after the first three or four years of school.[14]

Race and nationality influence the I.Q. but it is not clear whether the differences found are dependent primarily on hereditary or environmental factors. The highest average scores are obtained by children of English, Scottish, and Jewish descent. In all studies made in the United States, Italian and Polish children average uniformly low, but they achieve somewhat higher scores on nonlanguage tests than on those requiring more knowledge of English. On practically all tests Negroes are inferior in I.Q. to white children as a whole but they test somewhat higher than Italian and Polish children. The average I.Q. for Negro children tends to decrease as the age and grade increases and this has been interpreted to indicate the adverse effect of poor environment on the child. Studies indicate that less than 25 per cent of Negro children reach or exceed the median of white children. Chinese children in the United States test fairly high. Indian children score low, specially pure-blooded Indians, but Jamieson and Sandiford found they reached almost average level on certain tests not involving the understanding of the English language. It is probable that the tests used do not give a fair estimate of their ability because these children have lived in a different environment and have had different experiences than the white children for whom the tests are standardized. It should be clearly understood that in all racial and national groups there are individuals who test high, only the average or mean scores differing. It is impossible at present to estimate the intelligence of children in their native countries from these results, as immigration to the United States involves a highly selective factor.

Rural children score lower than city children. This difference decreases with the number of years of school attendance, indicating that at least part of the handicap is due to inadequate education and training.

Yerkes[15] found that, during the first World War soldiers from the Northern section of the country scored higher than those from the South. Race cannot account for this difference since the same results were obtained for both whites and Negroes. Possibly education was the important factor. Great differences were found between the average for soldiers from Oregon and from Mississippi; as great, in fact, as those found between Indians and whites. This wide variation is difficult to explain.

According to several observers the administration of Benzedrine leads to an improvement in performance on intelligence tests in most children. This probably results from an induced feeling of well-being, an increase in confidence and energy, greater alertness, and a greater desire to succeed.[16]

Infants born prematurely are somewhat inferior to full-term infants during the first year of life. This is less pronounced if correction is made for the time of prematurity. Smaller infants are more retarded than larger ones. On the average, infants with birth weight under 4 pounds (1.8 kg.) do not reach the average development of full-term children until the eighteenth month, whereas infants weighing more than 4 pounds overtake the normal group at about 9 months of age. Prematurely born infants are more retarded in motor and manipulative development than in intellectual content and social responsiveness.[17] In personal social behavior, as tested by the Gesell Developmental Inventories,

the performance of prematurely born infants was consistently relatively superior to full-term infants when account was taken of the amount of prematurity. This has been attributed to the unusual care and attention offered the prematurely born, to their closer association with adults, and to the fact that they have had an additional extrauterine period and therefore greater opportunity for training. At a later age the prematurely born give average scores on language tests which would make them somewhat superior if account is taken of the period of prematurity. Children of school age who have been born prematurely are in the majority of instances in the proper grade for their age, and their intelligence is similar to that of full-term children of like age.

Continued severe psychic trauma such as life in an undesirable institution or exposure to an unstimulating environment in the home leads to a decrease in the I.Q. in young children. Conversely, children reared in superior foster homes show higher I.Q.'s than might be expected from their original heredity and environment. Studies of identical twins reared apart have shown that the greater the difference in environment the greater the difference in I.Q. One must conclude from these studies that "extreme differences in educational and social environments are accompanied by significant differences in intelligence."[18]

Intelligence Resemblance in Families.—There is on the whole, a fairly close resemblance in the I.Q.'s of members of the same family (represented by a correlation coefficient of about .50). The resemblance between siblings and mother, and siblings and father is of about the same order. Terman found, in his follow-up study of gifted individuals, that the mean I.Q. of their offspring was 127.7. Though this average was about 24 points below that of the parents, it is much higher than that found in the general population. The incidence of children with feeble-minded and borderline mentality was low. On the other hand, the proportion of offspring with I.Q.'s of 150 or higher was twenty-eight times as great as that for unselected children.[19]

There is no definite correlation between I.Q. test results and health ratings, history of illnesses, body build, skeletal maturity (as measured by ossification of the bony centers), birth order, being an only child, broken homes, or excessive shyness.

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Comments on Current Literature

BONE INVOLVEMENT IN LEUCEMIA

PAIN along the bones and in the joints in the acute leucemias has not been stressed sufficiently. Similarities of symptomatology in leucemia and rheumatic fever have led to confusion and to real diagnostic difficulties. The coexistence of leucemia and rheumatic fever is regarded as rare. From the standpoint of management and of prognosis, the importance of early correct diagnosis is appreciated readily.

Aisner and Hoxie[1] in the *New England Journal of Medicine* for May 20, 1948, have reviewed pertinent material on this subject and have added four interesting cases of their own. They call attention to the fact that as early as 1889 Ebstein, and, in 1895, Fraenkel, considered pain and tenderness along the bones and in the joints a prominent feature of the symptomatology of leucemia. Since that time a number of writers on leucemia have emphasized this clinical point. In two of the four cases reported by Aisner and Hoxie, in which bone and joint manifestations were outstanding features, a diagnosis of acute rheumatic fever was made on admission to the hospital. In the third of the four cases, a diagnosis of subacute bacterial endocarditis had been made before admission, and in the fourth, the referring physician had diagnosed the case as rheumatic fever. Even early blood studies may be confusing since the blood picture of early leucemia may be within normal limits, and since nonleucemic children may produce immature white blood cells in response to severe infections. Bone marrow studies also may be nonrevealing in early leucemia.

The presence or absence of leucocytosis may be of some diagnostic aid, since leucocytosis is of general occurrence in active rheumatic fever associated with joint pain. According to Wilson[2] the white blood cell count varies between 8,000 and 23,000 and in 91 per cent of her cases the white blood cell counts were over 9,000. In this connection Aisner and Hoxie stress the differential count, stating that "leucopenia associated with symptoms referable to the bones and joints should make one suspect conditions other than acute rheumatic fever."

In rheumatic fever the differential count reveals an increase in the percentage of neutrophiles. Consequently the occurrence of lymphocytosis, especially when associated with leucopenia, suggests a diagnosis other than rheumatic fever. Two of the cases described by Aisner and Hoxie illustrate these clinical points. In discussing joint pain, these authors state that in conditions like leucemia in which there may be considerable destruction of blood elements and the liberation of nucleoprotein, the blood uric acid level may be elevated and this value in itself may be used as a differential diagnostic feature.

In a brief discussion of the x-ray appearance of the bones and joints in leucemia, these authors emphasize the wide variability in the roentgenologic aspects of the skeleton in leucemia. Changes in the bones may include subperiosteal elevation, cortical destruction, rarefaction, osteosclerosis and osteoporosis, the most common skeletal finding being periosteal elevation.

In the June (1948) issue of the *American Journal of Roentgenology and Radium Therapy,* Frederic N. Silverman[3] presents an extensive study of skeletal lesions in leucemia. In this report which carries a review of the literature, and is based on observations on 103 infants and children, Silverman states

that accurate diagnosis of leucemia in the pediatric subject which is often difficult, is aided considerably by roentgenologic studies of the skeleton. Silverman studied 131 patients with leucemia, on 103 of whom the roentgenologic studies were considered adequate. Fifty-two of the 103 leucemic children showed bone changes and four types of lesions were observed: transverse bands of diminished density, osteolysis, osteosclerosis, and subperiosteal new bone formation. Of forty-two patients who complained of bone pain, twenty-five had skeletal lesions demonstrable in roentgenograms.

In discussing differential diagnosis, Silverman states that in his experience the conditions most frequently confused with leucemia were, first, rheumatic fever, and second, secondary anemia. Still's disease and infectious mononucleosis were among the diagnoses considered in certain cases of leucemia. In his conclusion Silverman states that children showing anemia, fever, and pain in the extremities present a problem in differential diagnosis, and that the roentgen method often proves an aid in the diagnosis of acute leucemia.

In addition to rheumatic fever and leucemia, differential diagnosis of patients with bone and joint pain, particularly those in the pediatric age group, must include such conditions as undulant fever, poliomyelitis, osteomyelitis, scurvy, rickets, syphilis, gonorrhea, tuberculosis, Haverhill fever, Hodgkin's disease, and Still's disease. It is of great importance that, in addition to routine and careful examinations of the blood, all patients presenting bone and joint pain as symptoms should have careful x-ray studies in order to detect changes in the skeletal system.

RUSSELL J. BLATTNER

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News and Notes

Dr. James Goodfriend, Instructor of Pediatrics at Washington University Medical School, died of a heart attack Monday night, July 5, 1948.

Dr. John Aikman of Rochester, New York, died July 13, 1948.

Dr. Oscar Reiss of Los Angeles died suddenly on June 16, 1948, as he was preparing to leave for Chicago to preside at the meetings of the Section on Pediatrics of the A. M. A. of which he was chairman.

At the A. M. A. meeting of the House of Delegates in Chicago, on June 21, the Distinguished Service Medal of American Medical Association was awarded to Dr. Issac Arthur Abt. In honoring Dr. Abt for his lifetime of service to American Medicine, the Association has paid a well-deserved tribute to an outstanding pediatrician who is loved and respected by all.

The following were certified by the **American Board of Pediatrics** at the examination in Chicago, June 26 and 27, 1948:

Dr. John H. Cordes, Jr., 216 Empire Bldg., 302 Central Avenue, St. Petersburg, Fla.
Dr. Victor J. Cordes, 7405 Harwood Avenue, Wauwatosa 13, Wis.
Dr. Susan Coons Dees, Duke Hospital, Durham, N. C.
Dr. Harold X. Gerber, 1046 Wilson Avenue, Chicago 40, Ill.
Dr. John Roland Harvin, 206 North Sumter Avenue, Sumter, S. C.
Dr. Maurice Kaufmann, 2 Nassau Place, Hemstead, N. Y.
Dr. John T. Kometani, Tulane Medical School, Dept. of Pediatrics, New Orleans, La.
Dr. William Caldwell Layton, 2300 Ralston Avenue, Burlingame, Calif.
Dr. Jacob S. Light, 405 37th Place, S.E., Washington 19, D. C.
Dr. Bernard L. Lipman, Medical Arts Building, Philadelphia, Pa.
Dr. Dan Campbell McDougall, 210 Kane Building, Pocatello, Idaho.
Dr. Irving Howard Mauss, 443 Beach-138th Street, Belle Harbor, N. Y.
Dr. Evelyn E. Miller, 1642 Harrison Street, Philadelphia 24, Pa.
Dr. Dominic S. Motsay, 111 West Lockhart Street, Sayre, Pa.
Dr. Brian St. John Moynahan, 334 Washington Avenue, Belleville, N. J.
Dr. Harry Thomas Nagel, 518 South 5th Avenue, Maywood, Ill.
Dr. Louis J. Needels, 402 Loma Alta Drive, Santa Barbara, Calif.
Dr. Phyllis T. Mrazek Orland, 6628 West Cermak Road, Berwyn, Ill.
Dr. Herbert J. Palmer, 170 West 77th Street, New York City, N. Y.
Dr. John Lyman Peck, Johns Hopkins Hospital, Baltimore 5, Md.
Dr. Walter Pick, 42 Fox Street, Fitchburg, Mass.
Dr. Bernard C. Prietsch, 4752 Baldwin Manor Road, Pittsburgh, Pa.
Dr. Francis Lupton Robinson, Permanente Foundation Hospital, 280 MacArthur Blvd., West Oakland, Calif.
Dr. Joseph L. Rubel, 5 East Gregory, Pensacola, Fla.
Dr. Henrietta K. Sachs, 1820 Juneway Terrace, Chicago 26, Ill.
Dr. Joe M. Standefer, 934 42nd Street, Des Moines, Iowa.
Dr. Meritt W. Stark, Child Research Council, 4200 East 9th Avenue, Denver, Colo.
Dr. Walter Milton Tasem, 619 South Bonne Brae, Los Angeles, Calif.
Dr. Herbert Allan Wenner, University of Kansas Hospitals, Kansas City, Kan.
Dr. Norman C. Woody, Jr., 1430 Tulane Avenue, New Orleans 13, La.
Dr. Charles Richard Yoder, 705½ East Walnut Street, Bloomington, Ill.

At the meeting of the **Section on Pediatrics of the A. M. A.** in Chicago in June, the following officers were elected for 1948-1949:

Chairman: Woodruff L. Crawford, Rockford, Ill.
Vice-Chairman: Ambrose McGee, Richmond, Va.
Secretary: Margaret M. Nicholson, Washington, D. C.

Public health reports up to the last week of June show a definite increase in the incidence in poliomyelitis. As of July 10, 2,533 cases have been reported since the seasonal low week (the third week of March), as contrasted with 1,696 in 1946, and a five-year median of 1,027. The disease is in definite epidemic form in the widely separated states of North Carolina, Texas, and California. The New England area shows the lowest incidence as of July 1.

The **Nineteenth Annual Postgraduate Symposium on Heart Disease** of the San Francisco Tuberculosis Association will be held Oct. 27 to 30, 1948, at the St. Francis Hotel. The session on Wednesday afternoon, October 27, will discuss Heart Disease in Children. Eight papers will be presented by California pediatricians on the subject of rheumatism and operable congenital heart disease.

Dr. James N. Etteldorf has been appointed associate professor of pediatrics at the University of Tennessee Medical College at Memphis. He will be director of the pediatric research and diagnostic laboratory of the Gaston Hospital.

The **University of Colorado School of Medicine** and the Colorado State Department of Health announce a short course for physicians on problems of newborn infants, both premature and full-term, to be given at the University of Colorado Medical Center, Denver, Oct. 14 to 16, 1948, inclusive. The course is open to graduates of medical schools approved by the A. M. A. A registration fee of ten dollars ($10.00) is required. Inquiries should be directed to Frode Jensen, M.D., Director of Graduate and Postgraduate Education, University of Colorado Medical Center, Denver, Colo.

Book Reviews

Fundamentals of Human Reproduction. Edith L. Potter, M.D., New York, 1948, McGraw-Hill Book Co., Inc., 231 pages.

This concise book describing the background and embryology of human reproduction is well written. Its completeness affords an over-all picture of the course of events leading to the birth of the full-term baby, with the greatest emphasis on the cytology, biology, and embryology of the fetus.

There are three main divisions, of which the first two describe the general background and plan of the reproductive process, and the third is a detailed study of fetal organ embryology. There is a short fourth division pertinent to the birth and future life of the infant.

One of the outstanding features of the book is twelve beautiful black and white plates of fetal development ranging from the chorionic vesicle stage to total body x-radiography of the fetal skeleton. In addition, the diagrammatic illustrations accompanying the text are particularly commendable.

It would seem that the material is too exhaustively covered for this book to be used as a text for basic students of nursing, and that the real value of Dr. Potter's work will be for postgraduate students of nursing and nursing instruction, as well as for medical students, physicians, and students specializing in the field of embryology. MONAT.

Widening Horizons in Medical Education. A Study of the Teaching of Social and Environmental Factors in Medicine, 1948, The Commonwealth Fund, 228 pages. Price $2.75.

This is the report of a joint committee of the Association of American Medical Colleges and the American Association of Medical Social Workers, with Jean A. Curran, M.D., and Eleanor Cockerill as cochairmen. It is indicative of an important trend away from the purely technical and materialistic character of medical education which has dominated the medical school curriculum in the past twenty-five years, a situation which resulted from the tremendous advances in medical science and techniques during this period.

The committee visited and studied carefully the work in thirteen schools, and obtained from the others, by letter, information as to the extent which consideration of the social and environmental factors enters into the medical curriculum. Although there was no uniformity found in the method of approach or the extent or place of socioenvironmental teaching, it is most important and interesting to find that although the study took place during the accelerated period of medical teaching when the faculties were carrying an extraordinary teaching load, nearly every school was attempting to introduce instruction in this phase of medicine into the curriculum. Details are given of the methods used in many of the schools and of the special projects that have been set up by some. It is obvious from the report that the method of instruction is in a highly experimental state, and the report is of great value in showing what the different schools are doing. Undoubtedly in a few years experience will be gained as to how the subject can best be presented to the medical student. The report very wisely does not attempt to lay down any specific plans as to how this type of instruction should be carried out. The report is largely a description of what is being done in a number of schools and the recommendations and conclusions are general in nature.

It is refreshing to find that so many teachers in our medical schools are becoming interested in the patient as a human being subject to social and environmental conditions and stresses which play a most important role in his health and in the development and treatment of disease conditions. It is a thing the man in practice has learned from experience. It augurs well for the physician of the future that these factors are being integrated into the instruction of the medical student. To the reviewer it would seem as if pediatrics were an ideal place to emphasize the importance of social and environmental factors. It would be of great value to some departments if the part-time teachers were utilized more in developing this aspect of medical instruction, as their recognition of its importance is a very practical one. B. S. V.

Editor's Column

"THE CRADLE TO THE GRAVE"

IN THE column on the Social Aspects of Medicine the JOURNAL has recently presented two discussions of the British Medical Service Act which went into effect on July 5. Discussions with JOURNAL readers have made it evident that some failed to understand that the discussions covered but one phase of a general social security program, which has been dubbed "the cradle to the grave." The medical part of the program is the most controversial part and naturally is of most interest to JOURNAL readers. In order to give a better understanding of the whole program sponsored by the present labor government in Great Britain, we enumerate some of the nonmedical "benefits" which are an integral part of the Act. Perhaps this will explain to some extent the support the program received despite the opposition of a large part of the British medical practitioners who feel the medical care provisions are unworkable and unfair to physicians.

Sick benefits to workers. $5.20 a week for a single man, and $9.90 for a couple with one child.

Maternity allowances. $32.00 after the birth of a child to an unemployed mother, and $109.60 to employed mothers.

Children's allowances. $1.00 a week for each child after the first, regardless of whether the father is employed or unemployed.

Death grants. $80.00 for funeral expenses.

Industrial injury. $11.00 a week for single men and more for married couples.

Unemployment benefits for as long as 30 weeks. Single men $5.20 a week, $8.40 for a couple, and $1.50 for the first child.

Old age pensions of $5.20 a week for women 60 years of age or over and men 65 years of age or over.

These are in addition to free medical and dental care, hospitalization, and surgical and other specialist consultation.

The estimated cost is $300,000,000 a year, which is three times what the United States spends per capita on its social security program. Compulsory contributions from the wage earners amount to about $1.00 a week, and 85 cents contributed by the employer. This it is estimated will provide about half of the total cost with the remainder being provided from general revenue funds.

Inadequate facilities to carry out the medical plans will in all probability seriously effect the satisfactory working of the medical aspects of the plans. For example, there are only ten clinics for group practice in London as against an estimated need of 162 for medical care under the Act. From reports it would seem as if the promised free dental care, including dentures, was almost impossible to carry out to the satisfaction of the insured.

British experience with the program during the immediate coming years will be watched closely both by those who favor and by those who oppose the extension of government participation in the field of medical care.

B. S. V.